Universidade de Lisboa
Faculdade de Medicina

Clinical pharmacology of oral anticoagulants: pharmacoepidemiology, safety and pharmacoeconomics

Daniel Gomes Caldeira

Supervisors: Joaquim José Coutinho Ferreira, M.D., PhD
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PhD dissertation in Medicine, Clinical Pharmacology

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Preface

This dissertation is the result of research that was carried out at the Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine, University of Lisbon, and at the Joaquim Ferreira Lab (Farmacologia Clínica), Instituto de Medicina Molecular, Lisboa, Portugal.

The overarching goal of this series of projects was to increase the knowledge and emphasize the importance of oral anticoagulants, particularly in conditions such as atrial fibrillation (AF). The projects were directly supervised of Professor Joaquim Ferreira (Head of the Laboratory of Clinical Pharmacology and Therapeutics, and Clinical Pharmacology Unit) and Professor Fausto Pinto (Head of the Cardiology Department at CHLN (Centro Hospitalar Lisboa Norte), Head of the CCUL (Centro Cardiovascular da Universidade de Lisboa), and Dean of the Faculty of Medicine, University of Lisbon.

This dissertation is written in English, with an extended summary in Portuguese, as predicated in *Regulamento de Estudos Pós-graduados da Universidade de Lisboa* published in *Diário da República, 2.ª série - N.º 57 - 23 de Março de 2015*, as well as the rules for presentation of PhD dissertation thesis of Faculdade de Medicina da Universidade de Lisboa

This dissertation is divided into six chapters: an introductory chapter; an elaboration of the original research projects, organized into four chapters corresponding to the main fields of clinical pharmacology at a population level (pharmacoepidemiology; drug safety aspects such as comparative effectiveness research focusing on safety and pharmacovigilance; and pharmacoeconomics); and a final chapter with discussion and conclusions applying to the body of work.

Each individual research project has a Background, Methods, Results, and Conclusions, which are discussed in the end of each chapter.

Regarding the specific chapter contents, the first chapter is an overall introduction to the principles of thrombosis, oral anticoagulants, the main indications for oral anticoagulation, principles of population clinical pharmacology, an identification of gaps in the evidence concerning these topics, and the objectives of the dissertation.

The second chapter presents an overview of the pharmacoepidemiology of oral anticoagulants. This includes quantitative elements, namely the proportion of patients treated with oral anticoagulants, using atrial fibrillation as the reference therapeutic indication, and qualitative elements, namely a measure of disease control, and an evaluation of prescription patterns among Portuguese patients, particularly using Vitamin K Antagonists (VKA). The prescription of oral anticoagulants in Portugal was assessed over time in order to determine the impact of non-vitamin K antagonist oral anticoagulants (NOACs).

In the third chapter, the safety issues (both bleeding and non-bleeding adverse events) of NOACs and VKA were scrutinized through systematic reviews and meta-analyses of randomized controlled trials. Tolerability and acceptability (drug discontinuation) were additionally evaluated in this comparative effectiveness/safety chapter.

In the fourth chapter the safety of oral anticoagulants from a pharmacovigilance perspective were appraised. The safety evaluation of the oral anticoagulants was not restricted to the controlled setting (RCTs) but also included 'real world' observational research. The data presented in this chapter come from spontaneous reports of adverse drug reactions with oral anticoagulants in Portugal were analyzed in order to complement the evaluation from the RCTs.

The fifth chapter presents a pharmacoeconomic analysis of oral anticoagulants, with AF as the reference condition in terms of burden, cost, and cost-effectiveness of the different oral anticoagulants.

In the sixth and final chapter, the findings and their implications for clinical practice and research are addressed, along with final remarks.

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To the staff of the Unit of Pharmacovigilance of Lisboa and Vale do Tejo;
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List of abbreviations

95%CI: 95% Confidence interval.

AC: anticoagulants.

ACC: American College of Cardiology.

ADR: Adverse drug reaction.

AE: Adverse event.

AF: Atrial fibrillation.

AHA: American Heart Association.

ASA: aspirin;

ATC: Anatomical Therapeutic Chemical.

BID: Twice daily.

CRNM: clinically relevant non-major;

CRNMB: clinically relevant non-major bleeding

CU: Counting Units.

CV: Cardiovascular.

DALY: Disability-adjusted life years.

DDD: Defined Daily Dose.

DILI: Drug-induced liver injury.

DRG: Diagnosis-related Groups

ESC: European Society of Cardiology.

EU: European Union-

GI: Gastrointestinal.

GUSTO: Global Use of Strategies to Open Occluded Arteries.

HR: Hazard Ratio.

HS: hemorrhagic stroke.

ICD 9-CM: International Classification of Diseases, Ninth Edition, Clinical Modification.

ICER: Incremental cost-effectiveness ratio.

ICUR: incremental cost-utility ratio.

ICH: Intracranial hemorrhage.

INR: International Normalized Ratio.

IS: Ischemic stroke.

ISTH: International Society of Thrombosis and Haemostasis.

LMWH: Low-Molecular-Weight Heparin.

MARM-AF: Mechanical And Rheumatic Mitral valvular AF.

MI: Myocardial infarction

mRS: modified Rankin scale.

NHS: National Health Service.

NNT: Number needed to treat.

NNH: Number needed to harm.

NOACs: Non-Vitamin K Antagonist Oral Anticoagulants.

NVAF: non-valvular atrial fibrillation.

OAC: Oral anticoagulation.

OR: Odds ratio.

PAF: population attributable fraction

QALY: Quality of life-adjusted life years.

RCT: Randomized controlled trial.

RR: Risk ratio.

SAE: Serious adverse event.

SD: Standard deviation.

SPAF: Stroke prevention in atrial fibrillation.

TIMI: Thrombolysis in Myocardial Infarction

TTR: Time in Therapeutic range

ULN: Upper limit of normal.

VKA: Vitamin K Antagonists.

VTE: Venous thromboembolism.

WHO: World Health Organization.

Publications

Research projects

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See also Appendix: List of full publications and *Facsimile* of published articles.

ABSTRACT

INTRODUCTION

Oral anticoagulant drugs are essential in the treatment and prevention of thromboembolic events in certain prothrombotic conditions. Atrial fibrillation is the most prevalent arrhythmia, and is the main indication for chronic oral anticoagulation due to its thrombotic complications. Vitamin K antagonists (VKA) were until recently the only therapeutic options of this class in Portugal, namely in the form of warfarin and acenocoumarol. Despite proven efficacy, VKAs have a large pharmacodynamic variability owing to multiple potential interactions with food and other drugs. The development of the non-vitamin K antagonist oral anticoagulants (NOACs; apixaban, dabigatran, edoxaban, and rivaroxaban) increased the therapeutic armamentarium for anticoagulation. NOACs act directly by blocking thrombin or factor Xa, and exhibit an antithrombotic effect at least as effective as VKAs. Since the myriad of interactions found with VKAs are absent in NOACs, the anticoagulant effect is predictable, and does not require serial evaluations of hemostasis, making NOACs more convenient for patients and clinicians. Thus, it is reasonable to expect that NOACs may be prescribed often than VKAs. However, the approval of NOACs was based on phase III randomized controlled trials (RCTs), which are seldom planned to evaluate the safety of interventions. Additionally, NOACs are costlier than VKAs, raising the question of whether these new anticoagulants promote health gains at a sustainable cost to the Portuguese society. Therefore, it is important to better characterize the oral anticoagulants with a focus on NOACs in the population-level clinical pharmacology, namely pharmacoepidemiology, safety aspects of the oral anticoagulants (comparative safety and pharmacovigilance) and pharmacoeconomics.

OBJECTIVES

The aim of this dissertation was to improve the knowledge related to the oral anticoagulants in the four main fields population-level clinical pharmacology: pharmacoepidemiology, comparative effectiveness/safety, pharmacovigilance, and pharmacoeconomics.

Specific objectives:

1) Pharmacoepidemiology: To assess the state of oral anticoagulation in Portugal, in terms of proportion of non-anticoagulated patients, the quality of anticoagulation, and evolution of the prescription pattern since the licensing of NOACs.

2) Comparative effectiveness/safety research: To evaluate the safety of NOACs, based on clinical trials' data, in terms of bleeding and non-bleeding adverse events, as well as the overall tolerability and acceptability of the drugs.
3) Pharmacovigilance: To identify adverse events related to oral anticoagulants most frequently reported to Pharmacovigilance Units in Portugal.
4) Pharmacoeconomics: To assess the cost and burden of AF in Portugal, and the relative cost-effectiveness of oral anticoagulants in Portugal.

METHODS

To achieve the objectives, the following research projects were conducted:

1) Pharmacoepidemiology: A systematic review and meta-analysis of all published studies in Portugal assessing the prescription/use of oral anticoagulant therapy in patients with AF;

   A retrospective observational study of a cohort of patients treated with VKAs for assessment of anticoagulation control quality through the Rosendaal Time in Therapeutic Range (TTR);

   A retrospective observational study of national outpatient prescribing oral anticoagulants, with characterization of the number of boxes sold and Defined Daily Dose (DDD, a standardized measure of the World Health Organization) prescribed for each group of drugs.
2) Comparative effectiveness/safety research: Systematic review and meta-analyses based on aggregated data of phase III RCTs of NOACs compared to VKAs, for bleeding events, overall tolerability, and acceptability; and NOACs compared to all available comparators for non-bleeding adverse events. The data were pooled using a random-effects model, and expressed as relative risk (RR) with a confidence interval of 95% (95%CI).
3) Pharmacovigilance: A retrospective observational study of spontaneous reports related to oral anticoagulants, received by the National Pharmacovigilance System in Portugal.
4) Pharmacoeconomics: A study concerning the cost of illness and burden of AF, and a cost-effectiveness study of oral anticoagulants in Portugal for AF were performed. To the burden of disease assessment, disability-adjusted life years (DALYs) related to the AF were estimated, as well as both the direct (inpatient and outpatient) and indirect (lost productivity) associated costs. To evaluate the cost-effectiveness, a Markov model was used, with characteristics adjusted to Portugal. The relative costs and health

gains associated with NOACs were estimated and weighed through the Incremental Cost Effectiveness Ratio (ICER), which evaluates the cost of each Quality-Adjusted Life Years (QALY) gained for a given intervention in relation to the control intervention (VKAs and all NOACs).

RESULTS

1) About 60% of patients with AF in Portugal were not treated with oral anticoagulants, and oral anticoagulation with VKAs had a suboptimal control with a mean TTR of 61%, according with the single-centre retrospective study. Since the introduction of NOACs in the Portuguese market, the number of pack and DDD of oral anticoagulants prescribed increased significantly, this rise being due to NOACs. Currently the NOACs as pharmacological group have most of the market share of oral anticoagulants.
2) In the pooled safety data from phase III RCTs, NOACs were associated with a decreased risk of major bleeding (RR 0.72; 95% CI: 0.61 to 0.84; 12 RCTs), fatal bleeding (RR 0.52; 95% CI: 0.65 to 0.41; 12 RCTs) and ICH (RR 0.43; 95% CI: 12.36 to 12.51; 11 RCTs) compared to the VKA. Regarding major gastrointestinal, intraocular, and pericardial bleeding, there was no increase in the risk of these events.

   The NOACs are not associated with liver injury (RR 0.93; 95% CI: 0.75 to 1.15; 26 RCTs) or severe renal impairment (RR 0.93; 95% CI: 0.82 to 1.05; 7 RCTs). Similarly, there was no increased risk of infections or insomnia.

   The overall risk of serious adverse events was significantly decreased by NOACs compared to VKAs (RR 0.96; 95% CI: 0.94 to 0.98; 5 RCTs). The results for acceptability (drug discontinuation) were heterogeneous. However, for most NOACs the risk of treatment discontinuation due to drug-related or patient-related reasons were not increased compared to the VKAs in AF patients.
3) The Pharmacovigilance study data showed that most the reported adverse events were related to NOACs (78%). About 25% of these events were related to bleeding and 10% related thromboembolic events. The annual number of notifications has been increasing, but when adjusted to the degree of drugs exposure, the peak incidence was in 2012, with a subsequent decrease.
4) AF has an important burden in Portugal contributing to the yearly loss of 23084 DALYs and expenses of 141 million € (57% in direct costs and 43% in indirect costs). NOACs were shown to be cost-effective compared with VKAs for the prevention of

thromboembolic events in non-valvular atrial fibrillation. In the presented model, apixaban was shown to be cost-effective compared to warfarin (ICER €5529/ QALY) and dabigatran (ICER €9163/QALY), and dominant compared to rivaroxaban.

CONCLUSIONS

The proportion of patients receiving oral anticoagulant treatment is increasing in Portugal, mostly due to NOACs. These drugs have an acceptable safety profile, with an improvement of the risk of fatal and serious bleeding events, particularly intracranial hemorrhage, without substantial increase in other non-bleeding events, including hepatic, renal, or infectious. The risk of adverse events is generally lower, and most NOACs do not show an increased risk of discontinuation. Although most adverse events reported to the National Pharmacovigilance system are associated with the NOACs, the number of events since the increase in drug exposure has declined.

Atrial fibrillation, the main indication for oral anticoagulation, has an important burden, with costs related to the disease that account for about 0.1% of gross domestic product of Portugal. The NOACs use for stroke prevention in AF is cost-effective compared with VKAs.

Keywords: anticoagulation; pharmacology, prescription; safety; economics.

RESUMO

INTRODUÇÃO

Os anticoagulantes orais são essenciais no tratamento e prevenção de eventos tromboembólicos. A fibrilhação auricular (FA) é a arritmia mais prevalente e constitui a principal indicação para anticoagulação oral crónica para prevenção das suas complicações tromboembólicas. Até recentemente, os antagonistas da vitamina K (AVK), representados em Portugal pela varfarina e pelo acenocumarol, eram as únicas opções entre os anticoagulantes orais. Apesar da sua comprovada eficácia, verifica-se uma grande variabilidade no efeito farmacodinâmico devido às múltiplas interacções com outros fármacos e com os alimentos. O desenvolvimento e aprovação dos anticoagulantes orais independentes da vitamina K (NOACs; apixabano, dabigatrano, edoxabano e rivaroxabano) aumentaram as opções terapêuticas entre os anticoagulantes orais. Estes novos fármacos bloqueiam directamente a trombina ou o factor Xa e apresentam um efeito antitrombótico pelo menos tão eficaz como os AVK. Uma vez que o seu efeito anticoagulante é previsível, sem a multiplicidade de interacções que os AVK possuem, os NOACs não necessitam de avaliações seriadas da coagulação, sendo mais convenientes para os doentes e profissionais de saúde. Por estes motivos, é expectável que os NOACs venham a ser mais prescritos. Contudo a aprovação dos NOACs baseou-se nos ensaios clínicos controlados e aleatorizados (RCTs) de fase III, que raramente são planeados para avaliar a segurança das intervenções. Adicionalmente estes fármacos têm um preço superior aos AVK, pelo que é essencial determinar se esta nova classe de anticoagulantes orais condiciona ganhos em saúde a um custo sustentável para a sociedade portuguesa.

Logo, é importante caracterizar os anticoagulantes orais com especial interesse nos NOACs nas principais áreas da farmacologia clínica a nível populacional: farmacoepidemiologia, aspectos relacionados com a segurança dos fármacos (segurança comparativa e farmacovigilância) e farmacoeconomia.

OBJECTIVOS

O principal objectivo desta dissertação foi melhorar o conhecimento sobre os anticoagulantes orais nas quatro principais áreas da farmacologia clínica populacional: farmacoepidemiologia, efectividade/segurança comparativa, farmacovigilância e farmacoeconomia.

Objectivos específicos:

1) Farmacoepidemiologia: Avaliar o estado da anticoagulação oral em Portugal, em termos de proporção de doentes não-anticoagulados, a qualidade da anticoagulação e evolução do padrão de prescrição.
2) Efectividade/segurança comparativa: Avaliar a segurança dos NOACs, baseada em dados de ensaios clínicos, no que diz respeito a eventos hemorrágicos, não hemorrágicos e tolerabilidade global, assim como a aceitabilidade destes fármacos.
3) Farmacovigilância: Identificar os eventos adversos relacionados com os anticoagulantes orais mais frequentemente reportados às Unidades de Farmacovigilância de Portugal.
4) Farmacoeconomia: Avaliar o custo e a carga da FA em Portugal e o estudo comparativo de custo-efectividade dos anticoagulantes orais em Portugal.

MÉTODOS

Para o cumprimento dos objectivos foram executados os seguintes projectos:

1) Farmacoepidemiologia: Revisão sistemática com meta-análise de todos os estudos publicados em Portugal que avaliaram o uso ou prescrição de anticoagulantes orais em doentes com FA;

   Estudos observacional retrospectivo de um coorte de doentes tratados com AVK, para avaliar a qualidade do controlo da anticoagulação através do parâmetro *Time in Therapeutic Range* (TTR) estimado através do método de Rosendaal.

   Estudo observacional retrospectivo da prescrição nacional de anticoagulantes orais em ambulatório, com caracterização do número de caixas vendidas e Doses Diárias Definidas (DDD: Defined Daily Dose, uma medida padronizada da Organização Mundial de Saúde) dispensadas para cada grupo de fármacos.
2) Efectividade/segurança comparativa: Revisões sistemáticas com meta-análise dos RCTs de fase III comparando os NOACs com os AVK, para eventos hemorrágicos, tolerabilidade global e aceitabilidade, e dos NOACs com todos os comparadores disponíveis para os eventos adversos não-hemorágicos. Os dados foram agregados utilizando o método de efeitos aleatórios e expressos em risco relativo (RR) com o intervalo de confiança de 95% (IC95%).
3) Farmacovigilância: Estudo observacional retrospectivo das notificações espontâneas relacionadas com os anticoagulantes orais, recebidas pela Sistema Nacional de Farmacovigilância em Portugal.

4) Farmacoeconomia: Estudo de custo e carga da FA e estudo de custo-efectividade relativa dos anticoagulantes orais em Portugal. Para a carga da doença foram estimados os anos de vida ajustados à incapacidade (*disability-adjusted life years*: DALYs) relacionados com a FA, os custos directos (internamento e ambulatório) e os custos indirectos (perda de produtividade) associados. Para avaliação do custo-efectividade relativa dos NOACs comparativamentes com os AVK foi utilizado um modelo de Markov com características ajustadas a Portugal. Foram ponderados os custo e ganhos em saúde, e a sua ponderação através do *Incremental Cost Effectiveness Ratio* (ICER), que avalia o custo de cada QALY ganho para uma determinada intervenção em relação à intervenção de controlo, que foram os AVK.

RESULTADOS

1) Até recentemente, 60% dos doentes com FA em Portugal não estavam tratados com anticoagulantes orais. Os dados do controlo da anticoagulação oral com AVK revelaram um controlo subóptimo com um TTR médio de 61%. Desde a introdução dos NOACs no mercado Português, o número de caixas e DDD de anticoagulantes orais aumentaram significativamente à custa destes fármacos. Actualmente os NOACs como grupo farmacológico têm a maioria da quota do mercado dos anticoagulantes orais.
2) Em relação aos dados de segurança agregados dos ensaios clínicos, os NOACs estiveram associados a uma diminuição do risco de hemorragia *major* (RR 0.72, 95%CI: 0.61 to 0.84; 12 RCTs), hemorragia fatal (RR 0.52, 95%CI: 0.41 to 0.65; 12 RCTs) e hemorragia intracraniana (RR 0.43, 95%CI: 0.36 to 0.51; 11 RCTs), comparativamente com os AVK. Em relação aos riscos de hemorragia digestiva *major*, intraocular e pericárdica, não houve aumento significativo destes eventos.

   Os NOACs não estão associados a lesão hepática (RR 0.93, 95%CI: 0.75 to 1.15, 26 RCTs) ou lesão renal grave (RR 0.93; 95%CI: 0.82 to 1.05; 7 RCTs). De igual forma não houve aumento do risco de insónia ou infecções.

   O risco global de eventos adversos graves foi significativamente reduzido pelos NOACs comparativamente com os AVK (RR 0.96; 95%CI: 0.94 to 0.98; 5 RCTs). Os resultados para a aceitabilidade (descontinuação do fármaco) foram heterogéneos. No entanto para a maioria dos NOACs o risco de descontinuação terapêutica por motivos relacionados com os fármacos ou com o doente, não esteve aumentado comparativamente com os AVK.

3) Os dados do estudo de farmacovigilância demonstraram que a maioria dos eventos adversos notificados estavam relacionados com os NOACs (78%). Cerca de 25% desses eventos foram hemorrágicos e 10% tromboembólicos. O número anual de notificações tem vindo a aumentar, mas quando ajustadas ao grau de exposição dos fármacos, verificou-se um pico de incidência em 2012, com sucessiva diminuição desde então. Não foram identificados eventos não-expectáveis.
4) Em Portugal, a FA apresenta uma carga importante, contribuindo para a perda anual de 23084 DALYs e custos aproximados de 141 milhões € (57% em custos directos e 43% em custos indirectos).

   Os NOACs mostraram ser custo-efectivos comparativamente com os AVK para a prevenção de eventos tromboembólicos na FA não-valvular. No modelo apresentado, o apixabano mostrou ser custo-eficaz em relação à varfarina (ICER €5529/QALY) e ao dabigatrano (ICER €9163/QALY), e dominante em relação ao rivaroxabano.

CONCLUSÕES

A proporção de doentes tratados com anticoagulantes orais tem vindo a aumentar, essencialmente devido aos NOACs. Estes fármacos têm um perfil de segurança globalmente aceitável com redução do risco de eventos hemorrágicos fatais e graves, particularmente a hemorragia intracraniana, sem aumento substancial de outros eventos não-hemorrágicos, nomeadamente hepáticos, renais ou infecciosos. O risco de eventos adversos é globalmente inferior e a maioria dos NOACs não apresenta risco de descontinuação aumentado. Embora a maioria dos eventos adversos reportados ao Sistema Nacional de Farmacovigilancia esteja relacionado com os NOACs, o número de eventos ajustados ao aumento da exposição aos fármacos tem vindo a diminuir.

A FA, principal indicação terapêutica para anticoagulação oral, tem um carga importante e custos que correspondem aproxidamente a 0.1% do Produto Interno Bruto de Portugal. O uso de NOACs é custo-efectivo para a prevenção de AVC na FA, comparativamente com os AVKs.

Palavras-chave: anticoagulação; farmacologia; prescrição; segurança; economia.

Chapter I

Overall introduction

1.1. Hemostasis and coagulation

Thrombosis is a homeostatic and hemostatic essential process that leads to the formation of a clot plug that disables the leakage of blood from disrupted vessels.
Hemostasis leads to the formation of a thrombus and is the results of the concerted actions of the following processes: vasoconstriction, platelet activation, and activation of the coagulation (Figure 1).

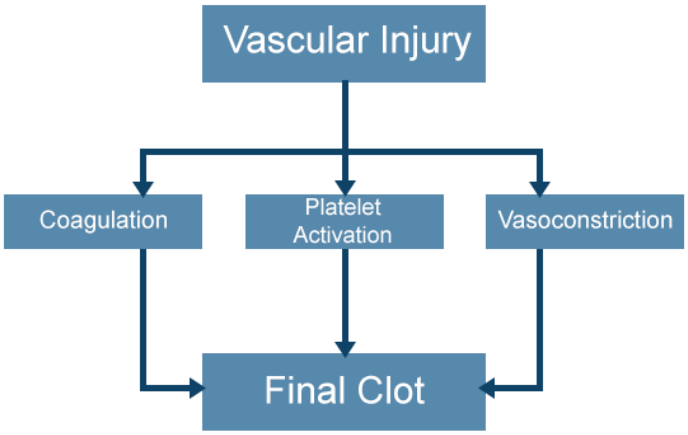

Figure 1: Physiologic hemostatic responses to vascular injury.

The physiology of coagulation may be explained by two models: the coagulation cascade model; and the cell-based model.

The classic coagulation cascade model is depicted in the Figure 2 and has three pathways: an extrinsic pathway, an intrinsic (or contact) pathway, and a final common pathway.

The final common pathway starts with the conversion of the factor X to its active form (Xa). Factor Xa, factor V and calcium establish the *prothrombinase* complex. At this point it is estimated that one molecule of Xa in the *prothrombinase* complex leads to the formation of 1000 thrombin (IIa) molecules[1], from prothrombin (II). Thrombin leads to increased platelet aggregation[1] and builds a plug of fibrin (activating the fibrinogen), furthermore promotes the

stability of the thrombus through the activation of XIII (to XIIIa) which covalently binds the fibrin molecules. Thrombin also promotes the activity of other coagulation factors (both from extrinsic and intrinsic pathways), inhibits the endogenous fibrinolytic system, and it is likely to have a role in inflammation/immunity[2].

Extrinsic pathway activation relies on the exposure of tissue factor (TF), which is constitutively expressed by vascular smooth muscle cells and adventitial fibroblasts, to factor VIIa in order to constitute the TF/VIIa complex, a major player in the activation of the common pathway by the formation of Xa factor.

The intrinsic pathway is classically described as the coagulation process activated by the exposure of negatively charged surfaces to plasma. This trigger leads to the formation of a complex kininogen and prekalikrein and factor XII with the sequential activation of the factors XII, XI, IX. Factor IXa and its cofactor VIIIa form the *tenase* which activates the factor X into Xa for the final common pathway.

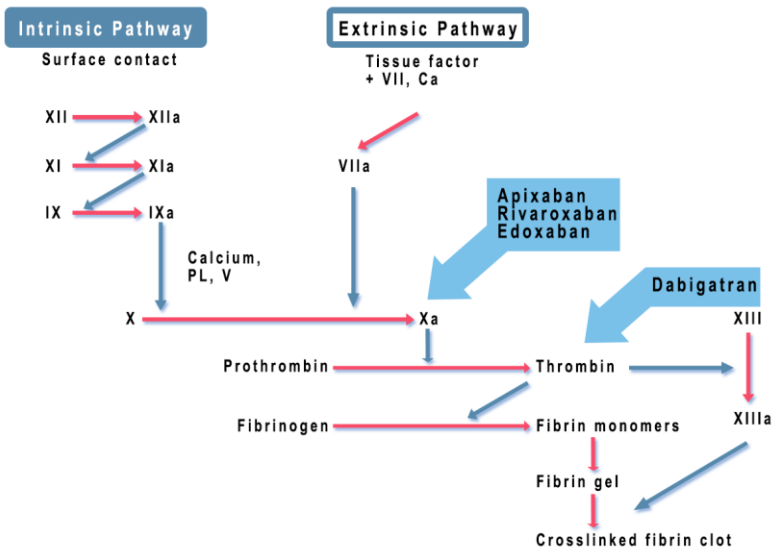

Figure 2: Cascade of coagulation.

The cell-based model is more contemporary, and undertakes the artificial division and step-wise fashion of understanding of the coagulation process. This model takes into account the role of platelets in the process and considers all the pathways of the classical classification to

occur (almost) simultaneously. The cell-based model is characterized by the following phases: initiation, amplification, and propagation (Figure 3) [3,4].

In the initiation, the complex TF/VIIa activates small amounts of factors IX, and X. The Xa and the available Va constitute the *prothrombinase* that activate of small amounts of prothrombin.

The amplification phase is characterized by the prothrombotic effects of prothrombin: platelet activation and release of factor V from alfa-granules; splits factor VIII from von Willebrand factor and activates it to VIIIa, thus leading to an increased downstream of the coagulation process with the activation of tenase (IXa from initiation, Va and VIIIa from amplification).

The propagation phase is characterized by a thrombin burst and requires that *tenase* complex, and *prothrombinase* complexes assemble in the platelet surface and generate further Xa and thrombin. At this stage, fibrinogen is converted to fibrin and stabilized through factor XIIIa.

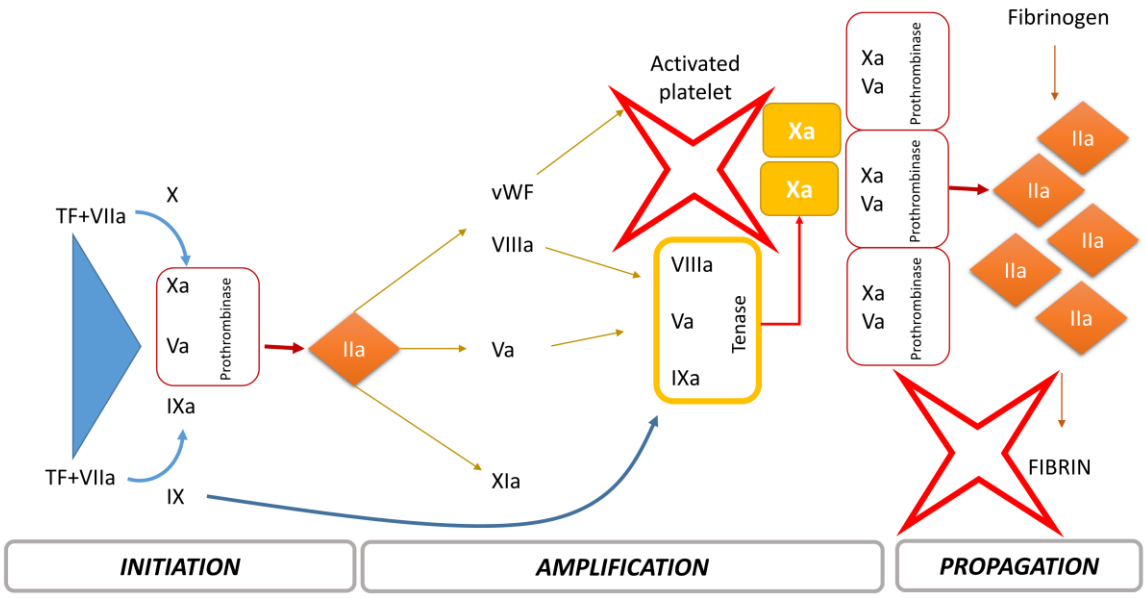

Figure 3: The cell-based model of coagulation.

These endogenous procoagulant routes are counteracted and regulated by the intrinsic anticoagulant processes in order to prevent the continuous coagulation and to maintain de homeostasis. The main interveners are the antithrombin, thrombomodulin, protein C and S, tissue factor pathway inhibitor (TFPI), and the endogenous fibrinolytic system.

Antithrombin, a circulating glycoprotein produced by the liver, binds to free and biologically active coagulation factors, and in larger extent to thrombin (IIa). Tenase and prothrombinase complexes are not adequately inhibited by antithrombin. Thus, antithrombin is thought to be important to limit the coagulation process to the site of vessel injury.

Thrombomodulin, a molecule expressed by endothelial cells, increases the rate of activation of protein C and its assembly with free protein S. Together protein C and S inhibit the factors VIIIa and Va, either free or as components of *tenase* and *prothrombinase* complexes, respectively.

TFPI is inhibits the formation of Xa factor (with protein S), and in the presence of large amounts of factor Xa, acts as a negative feedback modulator of the tissue factor pathway inhibiting the TF-VIIa complex.

The endogenous fibrinolytic system breaks down fibrin from clots through plasmin. Plasmin cleaves fibrin into fibrin degradation products. Thrombin inhibits the fibrinolytic system

These mechanisms are impaired in some patients, leading thus to hemorrhagic or prothrombotic conditions. Prothrombotic conditions may require anticoagulant drugs to dissolve thrombus (e.g. venous thromboembolism) or to prevent thrombus formation (e.g. atrial fibrillation).

Anticoagulant drugs may be classified according to the administration route: parenteral or oral. Parenteral anticoagulants include direct and indirect agents. Heparins (unfractioned and low-molecular weight) and fondaparinux are indirect agents as they require antithrombin and enhance the antithrombotic effect of this molecule. Direct parenteral anticoagulants inhibit specific coagulation factors without any further mediator. Bivalirudin and argatroban interfere with thrombin, and factor Xa is inhibited by otamixaban.

Due to the non-invasive nature of the administration route, oral anticoagulants are preferred for patients requiring medium- or long-term anticoagulation.
Oral anticoagulants are nowadays classified as Vitamin K Antagonists (VKA) or Non-Vitamin K Antagonists Oral Anticoagulants.
Vitamin K Antagonists include some drugs but in Portugal only warfarin and acenocoumarol are available.

As occurs with any new drug, anticoagulants are developed and studied in humans after their commercialization. Thus, it is important to further understand the principles of clinical pharmacology that mostly influence the approval and use of anticoagulants in the clinical practice.

1.2. Oral anticoagulants

Oral anticoagulants' classification can be divided into two classes according to the mechanism of action, i.e. if they depend or not of Vitamin K for the anticoagulant effect.

1.2.1. Vitamin K Antagonists

The Vitamin K Antagonists were, until recently, the only available oral anticoagulants. Nowadays there are different VKA (warfarin, acenocoumarol, phenprocoumon, fluindione), however only two of them are marketed in Portugal, warfarin (Varfine®) and acenocoumarol (Sintrom®).

VKAs were discovered in North America in the first quarter of the 20th century, when cattle started to become with a hemorrhagic illness during a period of deep economic crisis. The responsible for this illness was a specific hay, the sweet clover hay, which becomes infected by fungi such as *Penicillium*, when it becomes more humid. Such conditions allowed the transformation of coumarin to dicoumarol, which given to the cattle led to hemorrhagic signs 2 weeks after the ingestion, ending deadly in a period of 1-2 months [5,6]. The coumarin derivatives were extensively studied in the Wisconsin University by the Wisconsin Alumni Research Foundation (WARF) and one them was found to be particularly hemorrhagic for rat poisoning purposes with a faster onset of action compared to dicoumarol[6]. This drug was named WARFarin, commercialized in the United States as Coumadin® when clinical applications were discovered, and worldwide spread afterwards.

Vitamin K Antagonists can be classified as Coumarins or Indione derivatives. Warfarin, acenocoumarol and phenprocoumon are Coumarin derivatives. Fluindione and fenindione are Indadione derivatives. In Portugal, only warfarin and acenocoumarol are marketed.

Vitamin K Antagonists inhibit the Vitamin K epoxide reductase complex subunit 1 (VKORC1) (Figure 4). Vitamin K in the reduced form is a cofactor in the physiologic carboxilation of some coagulation factors produced in the liver such as II, VI, IX, C, protein C and S. VKAs inhibit the reduction of vitamin K and the substrate remains in the oxidized form disabling the adequate carboxylation of the referred factors through gamma-glutamyl

carboxylase (that requires reduced Vitamin K as a cofactor). Hence, coagulation factors are still produced but are biologically inactive producing the anticoagulant effect.

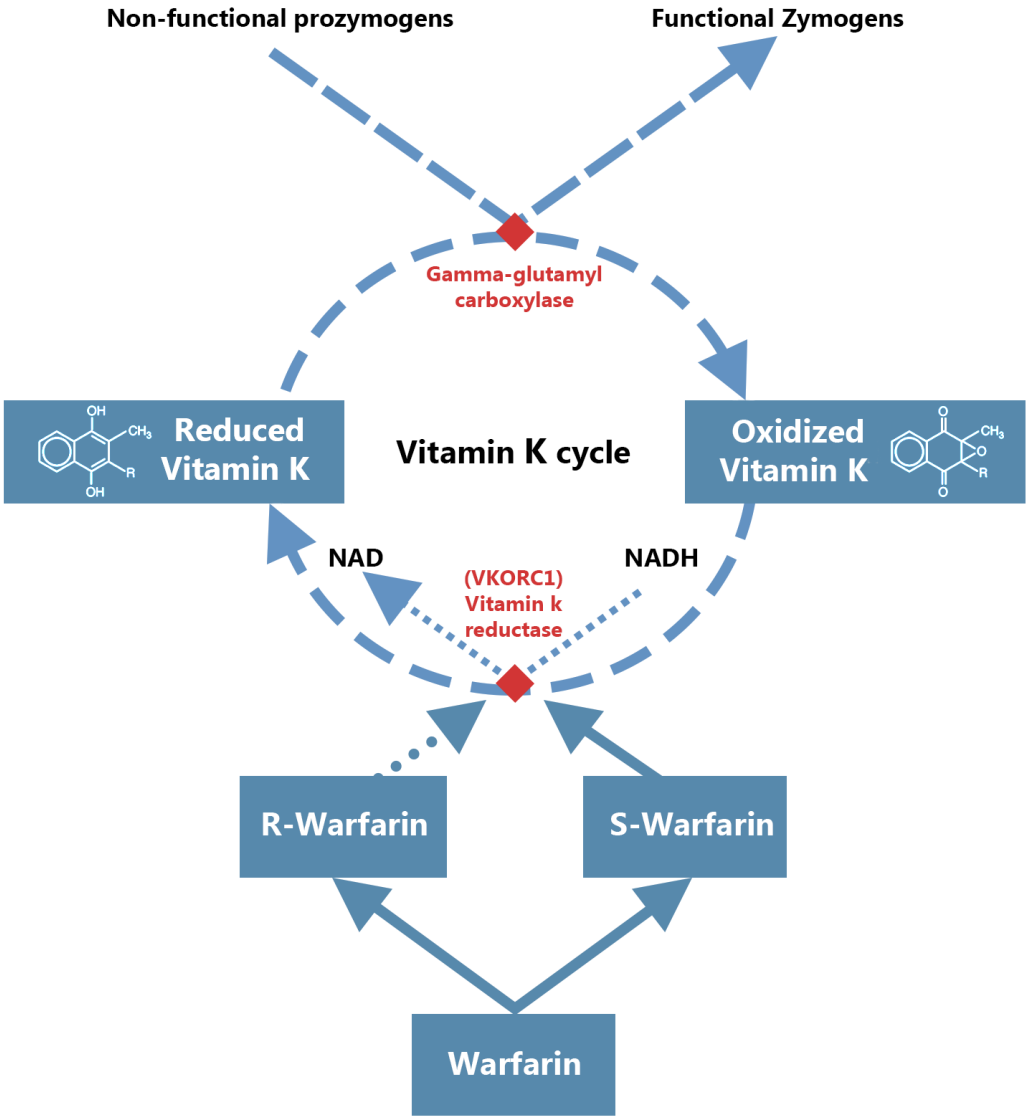

Figure 4: Mechanism of action of VKA (warfarin).

Warfarin is a racemic mixture of R- and S-warfarin, but the anticoagulant effect is predominantely caused by S-warfarin. On the other hand, the anticoagulation effect of acenocoumarol mainly depends on the R-enantiomer despite of S-enantiomer being more active due to its short half-life (1.8 h) compared to R-acenocoumarol (>6h)[7,8].

The metabolism is mainly hepatic through CYP2C9 and the excretion remains majorly renal. The main pharmacologic properties of warfarin and acenocoumarol are depicted in Table 1.

Table 1: Pharmacologic properties of VKAs, adapted from [9-11]

	*Single-pill dosage**	*Bioavaliability*	*Protein-binding*	*Hepatic Metabolism*	*Half-life*	*Excretion*
Warfarin	5 mg	100%	>99%	CYP2C9	40 h	Renal (metabolites)
Acenocoumarol	4 mg	96%	>98%	CYP2C9	8-11 h	Renal (metabolites)

* in Portugal; other countries may have pills with other dosages

VKAs pharmacodynamics are not linear, i.e. the administered dose may not be proportional to the anticoagulants effect, due to many clinical and genetic factors. The International Normalized Ratio (INR) is the measure used to evaluate the anticoagulant effect of VKAs. INR is a standardized method that uses the prothrombin time (time to clot formation after adding calcium and a thromboplastin to citrated plasma) and adjusts the laboratory result according to the thromboplastin used, in order to get uniform results irrespectively of the used method (INR = [prothrombin time/mean of normal prothrombin time]$^{\text{International Sensitivity Index of Thromboplastin}}$).

According to indication, patients are required to maintain in a range of INR values (mostly between 2.0-3.0). Therefore, regular INR checks should be scheduled, in order to change VKA dose whenever the INR value is out of the therapeutic range. When patients reach a stable period (same dose and therapeutics INR values) follow up and INR checks can be done monthly. Patients out of therapeutic range require more evaluations.

Up to 50% of the variability of warfarin maintenance dose may be attributed to genetic variation/polymorphism of CYP2C9 and VKORC1[12-14]. However, baseline clinical conditions, acute illness and drug-drugs interactions play an important role on the inter-individual and intra-individual variability of the anticoagulants effect.

Due to previously mentioned reasons the response to VKAs has an important inter-individual and intra-individual variability. Patients are required to maintain as possible the maximum of time within therapeutic range, however it is not frequent.

The most disseminated method to adequately estimate time in therapeutic range is the linear interpolation method of Rosendaal which assumes a linear variation of INR values between visits. It is accepted that a good quality of anticoagulation control is obtained when TTR>68-70%. Lower values of TTR (≤58-65%) are deemed to disclose an absence of protective effect of VKA compared to other treatments[15].

1.2.2. Non-vitamin K antagonist oral anticoagulants (NOACs)

The Non-Vitamin K Antagonists Oral Anticoagulants include the approved drugs apixaban, dabigatran and rivaroxaban, and edoxaban (awaiting evaluation for reimbursement by the national regulatory agency). This group was initially known as New/Novel Oral Anticoagulants and the acronym NOACs stood still. Some years after the development and approval of some of these drugs, they are no longer considered to be new or novel. Some claimed that these drugs should be called as Direct Oral Anticoagulants (DOACs) or Target-specific Oral Anticoagulants (TSOACs)[16,17]. In this thesis the acronym NOACs (from Non-Vitamin K Antagonists Oral Anticoagulants) was conserved as it reflects the differences compared to the previous established oral anticoagulants (VKA) [18].

NOACs selectively inhibit specific coagulation factors: dabigatran inhibits thrombin/IIa, Xa is inhibited by apixaban, edoxaban and rivaroxaban.

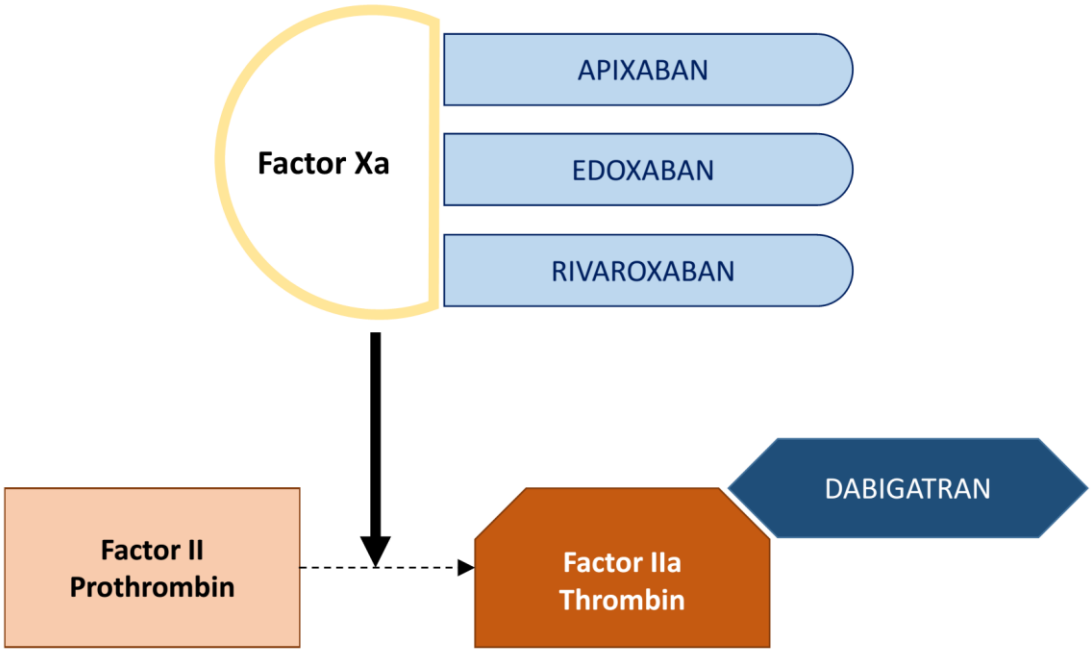

Figure 5: Local of action of NOACs. In light blue the Xa inhibitors, and in dark blue de thrombin inhibitor.

Table 2: Pharmacologic properties of NOACs

	Apixaban	*Dabigatran*	*Edoxaban*	*Rivaroxaban*
Prodrug	No	Yes	No	No
Mechanism of action	Xa inhibitor	IIa inhibitor	Xa inhibitor	Xa inhibitor
Bioavailability	50%	3-7%	62%	66-100%
Time to plasma peak	1-4 hours	2 hours	1-2 hours	2-4 hours
Half-life	12 hours	12-17 hours	9-11 hours	5-13 hours
P-Glycoprotein transportation	Yes	Yes	Yes	Yes
Hepatic metabolism	73%	Drug activation and 20% of active drug metabolism	50%	65%
CYP involvement	Minor CYP3A4	No	Minor CYP3A4	CYP 3A4 and CYP2J2
Renal clearance	27%	80%	35%	50%
Doses for AF and VTE	5 mg or 2.5 mg bid	150 mg or 110 mg bid	20 mg or 15 mg od; 15 mg bid in the first 3 weeks of VTE treatment with anticoagulants	60 mg or 30 mg od
*Indication for lower dose**	If 2 of the 3 following characteristics are present: ≥80 years-old; <60 Kg; Serum creatinine>1.5 mg/dL	≥80 years-old; HAS-BLED≥3; Verapamil use	Creatinine clearance 30–49 mL/min	Creatinine clearance 15–50 mL/min); ≤60 Kg; use of potent P-gp inhibitors

* Dabigatran's indication for 110 mg dose was retrieved from EU label.

Table 2 details some pharmacologic properties of NOACs [19,20].

Their oral route and absence of regular hemostatic parameters evaluation represent an evolution of anticoagulant treatment compared to parenteral anticoagulants such as Low-Molecular-Weight Heparin and VKA, respectively.

NOACs were approved by the regulatory agencies based on the findings of large randomized clinical trials (RCTs) showing that NOACs are at least non-inferior to control (VKA or low molecular weight heparins (LMWH) or aspirin). Atrial fibrillation represents the condition of the majority of candidates for NOACs use, and considering the reimbursement of the dabigatran, rivaroxaban and apixaban (the NOACs reimbursed in Portugal) for that condition, it is expected that the number of patients treated with these drugs will exponentially rise.

Antidotes specific for NOACs are also in development in order to further increase the healthcare and outcomes in bleeding patients. Idarucizumab is a humanized antibody fragment that binds to dabigatran and neutralizes its effect[21,22]. The first studies look promising although more data are required to ensure safety. Andexanet alfa is an antidote for Xa inhibitors and thus has the capacity to reversal the anticoagulant effects of apixaban, edoxaban and rivaroxaban[23-25]. Phase III study in patients treated with rivaroxaban is ongoing (ANNEXA-R trial, NCT02220725), while it is still just planned for edoxaban. The first phase III results for apixaban reversal with andexanet alfa (ANNEXA-A trial) look promising[25].

1.3. Main indications for oral anticoagulation

Oral anticoagulants prevent the formation of thrombi, and when thrombus or thrombi exist, these drugs prevent their expansion and also contribute to their resolution along with endogenous fibrinolysis.

Overall, oral anticoagulants are licensed for the prevention of stroke and other thromboembolic events in atrial fibrillation and in patients with prosthetic heart valves; prevention and treatment of venous thromboembolic disease. Other indications correspond to rare diseases such as antiphospholipid syndrome or pulmonary arterial hypertension[26], while in patients heart failure with low left ventricular ejection fraction no anticoagulant treatment should be prescribed in the absence of other indications[27].

The VKA treatment and INR target depends on the prothrombotic condition. In most conditions the INR target is 2.5 (range 2.0-3.0), but it can be higher in mechanical heart valves with additional clinical risk factors (Table 3).

Table 3: INR target according to indication.

Indication	*INR range or target*
Atrial Fibrillation	2.0-3.0
Mitral stenosis with AF, thrombus or LA diameter>55mm*	2.0-3.0
Bioprosthetic valves in sinus rhythm	2.0-3.0
Mechanical heart valves	Medtronic Hall, St. Jude Medical, Carbomedics AVR: 2.5 (+0.5)* Bjork-Shiley and bileaflets: 3.0 (+0.5)* Omniscience, Starr Edwards: 3.5 (+0.5)*
Venous thromboembolism	2.0-3.0
Left ventricular thrombus	2.0-3.0

* Suggested by the ACCP guidelines

** In the presence of risk factors for thrombosis such as AF; mitral, pulmonary or tricuspid valve replacement; enlarged left atrium; spontaneous echo contrast; mitral valve gradient; or LV systolic dysfunction

NOACs were tested in many prothrombotic scenarios. These drugs were overall approved for non-valvular AF, treatment and prevention of VTE recurrence, thromboprophylaxis after elective hip or knee arthroplasty, and rivaroxaban 2.5 mg twice daily was approved for secondary prevention in patients in acute coronary syndromes (Table 4).

Table 4: Main trials of NOACs according to indication and control group.

Indication	Main trials	Control	Approval by EMEA
Non-valvular AF suitable for VKA	Apixaban: ARISTOTLE Dabigatran: RE-LY Edoxaban: ENGAGE AF Rivaroxaban: ROCKET AF	VKA	Yes
Non-valvular AF in patients unsuitable for VKA	Apixaban: AVERROES	Acetylsalicylic acid	Yes
Thromboprophylaxis in patients with MHV	Dabigatran: RE-ALIGN (phase II RCT)*	VKA	No
VTE treatment and prevention of VTE recurrence	Apixaban: AMPLIFY Dabigatran: RE-COVER, RE-COVER II, RE-MEDY Edoxaban: Hokusai-VTE Rivaroxaban: EINSTEIN trials	VKA±LMWH	Yes
VTE prophylaxis after hip or knee arthroplasty	Apixaban: ADVANCE trials Dabigatran: RE-NOVATE trials, RE-MODEL, RE-MOBILIZE Edoxaban: STARS trials Rivaroxaban: RECORD trials	LMWH	Yes
VTE prophylaxis in acutely ill medical inpatients	Apixaban: ADOPT Rivaroxaban: MAGELLAN	LMWH	No
Acute coronary syndromes	Apixaban: APPRAISE-2 Rivaroxaban: ATLAS ACS-2 TIMI 51	Placebo	Only rivaroxaban 2.5 mg

* Nearly 30% of the patients with mechanical heart valves had AF or atrial flutter.

1.3.1. Atrial fibrillation

Atrial fibrillation, due to incidence, prevalence, and requirement of life-long anticoagulation in most of the patients, represents the condition owing the most important share of patients treated with oral anticoagulants. Therefore, atrial fibrillation was the target condition for most of the evaluations regarding the pharmacoepidemiology, safety and relative cost-effectiveness of oral anticoagulants.

AF is an important risk factor for stroke and it is the most frequently determined mechanism for ischemic stroke.[28,29] Over 15% of strokes are due to AF and they are generally more severe than those not related with AF.[30,31] Stroke attributable to AF is associated with a 30-day mortality of 25% and one-year mortality of 50%.[30] These patients have longer hospital stays and greater use of health resources compared to non-AF stroke patients.[32,33]

This a cardiac arrhythmia characterized by the absence of organized atrial electric activity and subsequent atrial contractility. This leads to a blood stasis in the atrial chambers prone to thrombus formation in the atria and these thrombi are the cause of stroke in 2/3 of patients with AF[34].

The approach and management of AF patients require an accurate clinical and electrocardiographic diagnosis, and should further include the adequate assessment of symptoms, impact in quality of life and concomitant comorbidities.
Treatment is mainly based on anticoagulant drugs (when indicated), choosing rate or rhythm control strategies, and optimization of comorbidities' treatment.

Oral anticoagulation is recommended for all patients with AF except those with very low thromboembolic risk. Patients with valvular AF (with significant mitral stenosis or mechanical heart valves) have a high thromboembolic risk, and should be treated with VKA (the only trial with NOACs in patients with mechanical heart valves – RE-ALIGN - showed increased risks of thromboembolic and hemorrhagic risks). Patients with non-valvular AF, require thromboembolic risk stratification. The CHA_2DS_2-VASc score allows the determination of the annual risk of thromboembolism (Table 5). Patients with CHA_2DS_2-VASc≥2 (annual risk of thromboembolic events ≥2%) should be anticoagulated.

Table 5: Components of thromboembolic risk stratification score CHA_2DS_2-VASc.

Clinical feature	Points
Congestive heart failure	1
Hypertension	1
Age (≥75 years)	2
Diabetes	1
Stroke or systemic embolism	2
Vascular disease	1
Age (65-74 years)	1
Sex category (female)	1

Antithrombotic drugs in AF

Stroke and systemic embolism are the main complications of AF.

VKA were appraised in many trials in AF patients. VKA reduced the risk stroke compared to the absence of antithrombotic drugs and antiplatelet drugs. The pooled results of 6 RCTs with 2900 patients determined a significant 64% stroke risk reduction with VKA compared to controls, and compared to antiplatelet drugs the dimension of stroke risk reduction was 22% (8 trials with 4876 patients).[35] In comparative trials VKA had a pooled 39% reduction in stroke risk compared to antiplatelet drugs (12 trials with 12963 patients).[35] A post-hoc analysis of Stroke Prevention in Atrial Fibrillation (SPAF) trials suggested that VKA reduces stroke risk, generally due to cardioembolic events, while acetylsalicylic acid mostly decreased the non-cardioembolic strokes in AF patients.[34]

The efficacy of VKA in AF was also stated in ACTIVE-W trial, where VKA reduced the risk of stroke compared to double antiplatelet therapy (acetylsalicylic acid and clopidogrel), with similar major bleeding risk.[36]

More recently, NOACs challenged VKA, and stroke/systemic embolism risk was at least non-inferior to VKA (apixaban and dabigatran 150 mg were superior to VKA) (Table 6).

Table 6: Pivotal trial of NOACs *versus* VKA in non-valvular AF

NOAC	***Apixaban***	***Dabigatran***	***Edoxaban***	***Rivaroxaban***
Acronym of pivotal trial	ARISTOTLE	RE-LY	ENGAGE AF-TIMI 48	ROCKET AF
Patients	18 201 patients with non-valvular AF	18 113 patients with non-valvular AF	21 105 patients with non-valvular AF	14 264 patients with non-valvular AF
Type of AF excluded (as per non-valvular definition)	Clinically significant (moderate or severe) mitral stenosis and mechanical heart valves	Hemodynamically relevant valve disease and prosthetic valves	Clinically significant (moderate or severe) mitral stenosis, unresected atrial myxoma, and mechanical heart valves	Hemodynamically significant mitral valve stenosis, prosthetic heart valves
Mean age	70 years	72 years	71 years	73 years
Mean CHA_2DS/ CHA_2DS_2-VASc	2.1	2.1	N/A	3.47
Mean follow-up	1.8 years	2.0 years	2.8 years	1.9 years
Primary efficacy outcome	Stroke and Systemic Embolism	Stroke and Systemic Embolism	Stroke and Systemic Embolism	Stroke and Systemic Embolism
Mean TTR in VKA arm	62.2%	64.4%	64.9%	55.2%
Stroke and Systemic Embolism, HR [95%CI]	0.79 [0.66-0.95]	150 mg: 0.65 [0.52-0.81]; 110 mg: 0.90 [0.74-1.10]	60 mg: 0.87 [0.73-1.04]; 30 mg: 1.13 [0.96-1.34]	0.88 [0.73-1.03]
Ischemic stroke*, HR [95%CI]	1.02 [0.81-1.29]	150 mg: 0.75 [0.58-0.97]; 110 mg: 1.13 [0.89-1.42]	60 mg: 1.00 [0.83-1.19]; 30 mg: 1.41 [1.19-1.67]	0.94 [075-1.17]
Major Bleeding, HR [95%CI]**	0.69 [0.60-0.80]	150 mg: 0.93 [0.81-1.07]; 110 mg: 0.80 [0.70-0.93]	60 mg: 0.80 [0.71-0.91]; 30 mg: 0.47 [0.41-0.55]	1.04 [0.90-1.20]

* For ARISTOTLE and RE-LY the estimates are for ischemic and uncertain type of stroke.

** Major bleeding defined according to ISTH.

CI: Confidence Interval; HR: Hazard Ratio.

In patients deemed to be unsuitable for VKA, acetylsalicylic acid has been taken as a valid option.[37] Double antiplatelet therapy has shown to decrease the risk of major cardiovascular events, particularly stroke, but major bleeding rates were significantly higher.[38] Thus the trend for adding clopidogrel on top of acetylsalicylic acid depends on individual ischemic/hemorrhagic assessment. More recently, AVERROES study (that was prematurely

halted due to the significance of differences found) showed that apixaban was superior to acetylsalicylic acid in the prevention of stroke or systemic embolism, without increasing the major bleeding risk.[39]

Patients with mitral stenosis have been excluded from trials and NOAC treatment cannot be recommended for these patients with increased embolic risk.

Patients with mechanical heart valves (with or without AF) are also considered out of the scope of NOACs due to the high thromboembolic risk retrieved from the phase II RCT RE-ALIGN with dabigatran[40]. Labile inflammatory and prothrombotic post-operative state, because of platelet activation and tissue factor release from surgery, were suggested as possible explanations[41,42]. Therefore, NOACs are not indicated for valvular AF, particularly those with 'mechanical and rheumatic mitral valvular AF', also termed MARM-AF, because patients with other forms of native valvular disease and bioprosthetic valves were already included in the main trials, and there was no safety warning regarding these conditions[42].

Atrial fibrillation in Portugal

The management of stroke risk factors should be taken seriously, particularly in Portugal where stroke is a significant cause of morbidity and mortality surpassing the coronary heart disease.[43]

The FAMA study provided a deeper insight about atrial fibrillation in the Portuguese population. In this cross-sectional study, a representative sample of the Portuguese population (≥40 years-old) with more than 10 000 individuals was screened with ECG for AF. The prevalence of AF was 2.5% (10.4% in patients with ≥80 years old), but only 1.6% of the individuals were aware to have this condition. Among patients aware of their condition, only 38% were treated with anticoagulants.

The FAMA study has brought knowledge about the prevalence of AF which is estimated to exist 121000 patients with this condition in Portugal. Nevertheless, data about anticoagulation in Portuguese patients are scarce and should be further evaluated.

1.4. Clinical pharmacology approach of oral anticoagulants

1.4.1. Principles of Clinical Pharmacology – Population applications

Clinical Pharmacology studies all aspects that relates drug development and human use [44]. According to the Aronson's manifesto for clinical pharmacology, the operational definition of this discipline includes four systems:

Two basic *"bench"* tools of human pharmacology:

- Core human pharmacology;
- Core applied pharmacology;

Two clinical / *"bedside"* applications of pharmacology:

- Individual application of clinical pharmacology;
- Population application of clinical pharmacology;

Core human pharmacology is closely related to the study of receptors, enzymes, transporters and autacoids, while core applied pharmacology overviews the cell pharmacology, drug metabolism, pharmacogenetics and pharmacokinetics[44]. .

The practical clinical fields are those required and most often evaluated for the approval of drugs and establishment of policies, as well as for drugs prescription and use in daily practice patients. While individual applications of clinical pharmacology study clinical toxicology, adverse reactions, drug interactions, drug monitoring and the practical aspects of drugs therapy in the individual patients, population applications have 4 main fields: Pharmacoepidemiology, Comparative effectiveness/safety research, pharmacovigilance and pharmacoeconomics (Figure 6).

The population applications are essential for the clinical practice as these provide and appraise evidence about interventions that may improve healthcare outcomes. The use and translation of the population applications to the individual clinical practice is provided by Evidence Based Medicine and Healthcare policies (approval, reimbursement) (Figure 6).

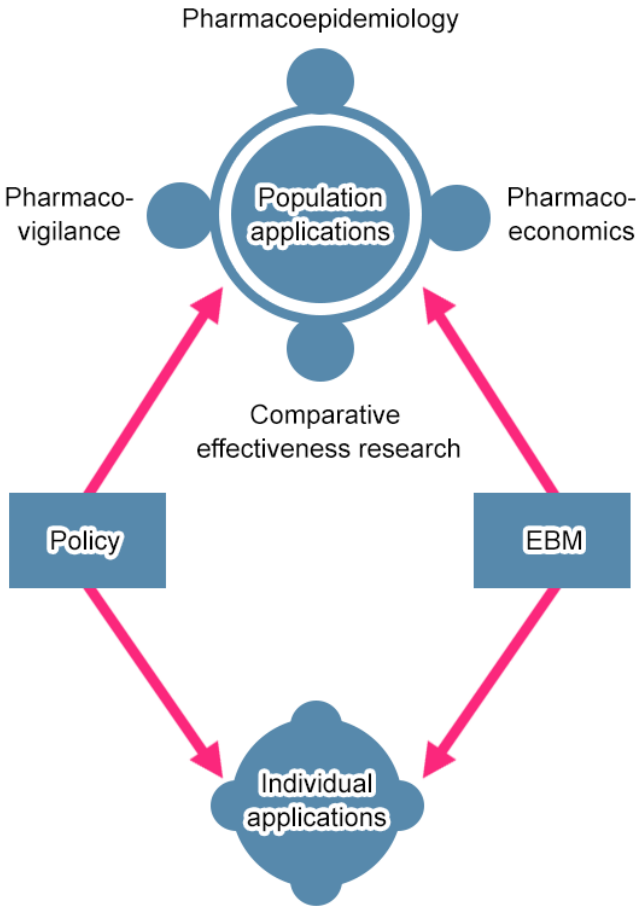

Figure 6: Interaction between population and individual applications of Clinical Pharmacology (adapted from Aronson et al.[44]).

In this dissertation, the research projects followed these four main areas of population clinical pharmacology, which considers pharmacoepidemiology, safety aspects in clinical trials (comparative safety reseach) and in the 'real world' (pharmacovigilance), and pharmacoeconomics.

1.4.2. Pharmacoepidemiology

Pharmacoepidemiology is widely defined by the World Health Organization as the study of the use and effects/side-effects of drugs in large numbers of people with the purpose of supporting the rational and cost-effective use of drugs in the population thereby improving health outcomes[45]. Although this definition may overlap with other domains, the prescription and use of drugs in populations is still exclusive of Pharmacoepidemiology. Pharmacoepidemiology of oral anticoagulants aims to identify the patterns use of oral anticoagulants. In this regard the proportion of patients requiring anticoagulation that are treated with these drugs (using AF as the model of disease) is a performance measure of healthcare delivery, that should be assessed. This is particularly relevant because the use of oral anticoagulants, including NOACs, is very heterogeneous due to obstacles related to physicians, patients, and financial status[46]. As previously seen, not all oral anticoagulants are similar, and VKA require dose changing when the INR is out the therapeutic range. Another measure of adequacy of drug use, particularly VKA, is the Time in Therapeutic Range (TTR), i.e. the time in percentage that patients stay within the therapeutic range.

1.4.3. Comparative effectiveness and safety research

The basis for the evaluation of the individual and population applications of drugs is the Evidence-Based Medicine (EBM). According to David Sackett, EBM relies on the conscientious, explicit, and judicious use of the best evidence to making decisions about the care of individual patients, taking into account the individual clinical expertise and the best available external clinical evidence from systematic research.[47] It aims to optimize the decision-making according to three major components the physician (with his knowledge and experience), the interventions/drugs (and their systematically retrieved evidence – CER data), and patients' values and preferences.

Thus, CER aims to generate and synthetize evidence that evaluates the effectiveness, benefits and harms of therapeutic interventions, diagnostic test, or healthcare frameworks.[48] The synthetized data is deemed to help patients, healthcare personnel and policy makers to make informed decisions at the individual and population levels.[48]
Data synthesis can have multiple sources, but currently the gold-standard for the evaluation of interventions are the systematic reviews and meta-analysis (Figure 7).

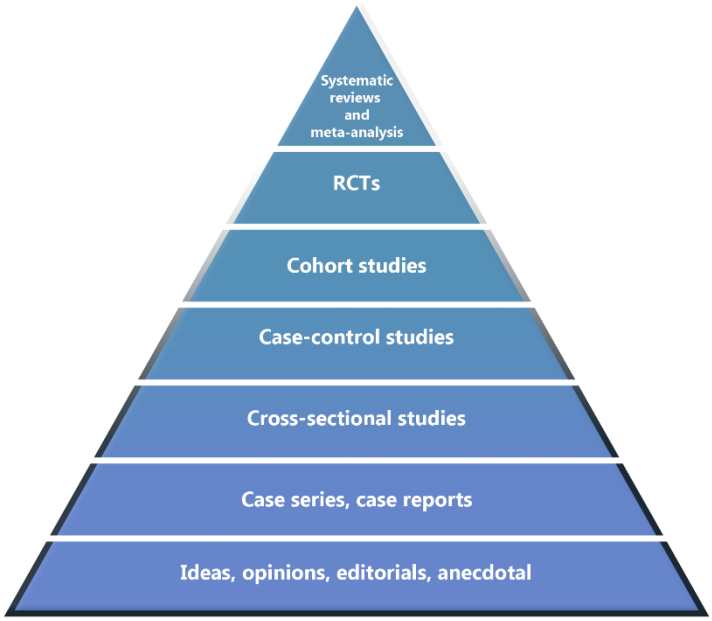

Figure 7: Evidence-based Medicine pyramid of publication types.

Systematic reviews of randomized controlled trials and meta-analyses are used to synthetize the data efficacy and safety. These are used to address and support the efficacy of oral anticoagulation in atrial fibrillation[35] and to dismiss the routine use of oral anticoagulants in patients with heart failure and sinus rhythm[27].

It is well established that RCTs are the most robust study design to investigate causality of therapeutic interventions and therefore they are positioned at the top of evidence hierarchies. However, RCTs are majorly powered for efficacy outcomes and *pivot* trials aim to produce the necessary evidence for drug approval (and reimbursement). The methodological caveats of RCTs, in particular the fact that they are rarely designed to evaluate safety, made them susceptible to limitations that may hamper their ability to fully characterize drug-related harms[49]. Among other reasons, by increasing the power to detect differences between groups, systematic reviews with meta-analysis of RCTs focusing on drug safety and tolerability are partially capable to overcome this limitation. Furthermore, they are particularly relevant before massive post-marketing use of a new drug (a stage where no real big world data is still available) as they generate the best evidence to evaluate safety and tolerability at this early stage.

Safety evaluates the freedom from harm or damage resulting from adverse reactions or physical, psychological, or behavioral abnormalities that occur as a result of drug use.[50]
The main safety concerns potentially raised by oral anticoagulants are related to bleeding complications, which are direct pharmacodynamics consequences of anticoagulants. Nevertheless, other adverse events such as liver injury, particularly after recent history of the oral IIa inhibitor ximelagatran post-marketing withdrawal due increased risk of liver injury[51], and other possible off-target effects must be scrutinized in order ensure the *primum non nocere* principle for a safe drug prescription.
The safety and efficacy of any chronic treatment, anticoagulation included, strongly depends on patients' tolerability and adherence to the medication.

1.4.4. Pharmacovigilance

Pharmacovigilance relies on the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.[52]

In oral anticoagulants, particularly after the licensing of NOACs, the post-marketing stage is crucial to screen for adverse events and to improve the awareness of the safety in a non-selected population, in opposition to clinical trials. Pharmacovigilance uses methods that can raise alerts through safety signals detection, which can be important for unexpected or rare adverse events. For example, a pharmacovigilance study has raised a warning regarding the existence of the risk of eosinophilia and systemic symptoms associated with fluindione (a VKA marketed in France).[53] Other firstly unsuspected adverse events related with VKA, are also target of studies such as osteoporosis or vessels calciphylaxis.

Furthermore, clinical trials are performed for 'short-term' outcomes, while the safety of using of new drugs for longer periods remains unknown.

1.4.5. Pharmacoeconomics

Economic/Pharmacoeconomic evaluations provide information for healthcare decision-makers, allowing optimal allocation of limited resources. In order to pursuit the impact of oral anticoagulants in the society, a burden of disease and cost of illness of atrial fibrillation and cost-effectiveness studies of oral anticoagulants were performed.

Burden of disease is estimated by the means of quality-adjusted life-years (QALYs) lost or disability-adjusted life years (DALYs), which is a measure of the years of health lost due to disease or premature death. QALYs are the product of life expectancy combined with a measure of the quality of life-years remaining. It accounts for non-fatal morbidities and their contribution to premature death. QALYs expresses lost health in time units, concealing the years-loss due to disability and period between death and standardized average life expectancy (years of life lost because of premature mortality).
QALYs lost or DALYs were calculated through standard methods,[23,25] with coefficients of disability that range from 0 (healthy) to 1 (full disability or death).[26]
The cost of atrial fibrillation included both direct and indirect costs.
Direct costs included hospitalization and ambulatory-related expenditures. Hospitalizations were derived from database of National Health Service (NHS) with diagnosis-related groups (DRGs). Outpatient care resource use was estimated by a geographically representative expert panel of various specialists.
Indirect costs assume that atrial fibrillation and related complications may disable patients for work and this brings a loss of economic value.

The relative cost-effectiveness and cost-utility approach of oral anticoagulants looked for the projection of anticoagulants impact in 'real world' conditions. The outcomes are the incremental costs, life-years gained, incremental QALYs and incremental cost-effectiveness ratio (ICER). ICER is calculated through the ratio of the difference in the cost between interventions and the difference in the outcomes, such as stroke, intracranial hemorrhage and mortality. ICER provides the cost that, on average, the intervention needs to obtain additional success (life years gained or QALY). For example, a ICER of €1000/QALY reflects additional cost with an intervention required to gain 1 QALY.

This is of paramount importance in the evaluation of interventions that provide health benefits but are more expensive than the available options. ICER determines the investment that it is required to gain standardized health units, such as incremental life-year gained or incremental QALY. In Portugal the limit usually taken to be acceptable for funding new health technologies (cost-effectiveness threshold / willingness to pay limit) is €20000/QALY.

1.5. Gaps in the evidence

Oral anticoagulants are efficacious in the many conditions, and NOACs overcome VKA regarding some unmet medical/patient needs. NOACs showed to be at least as efficacious as VKA in regards to stroke prevention in atrial fibrillation (as well as in VTE treatment; Table 4) leading to the approval, and thereby increasing the therapeutics options for these conditions.

Before the beginning of this project, the *status quo* of anticoagulation in Portugal was not well defined. Publications from other countries suggest that many patients were undertreated or were not adequately controlled with VKAs. In Portugal, the data about the proportion of patients that were anticoagulated were very scarse and underpowered, and the quality of control of VKA in Portuguese patients using standardized methods (such as Rosendaal method) was unknown. Due to their overall characteristics, NOACs are attractive and the control of anticoagulation would no longer be a problem, and it would be interesting to study whether simple indicators such as the prescription of anticoagulants would improve.

It is well established that RCTs are the most robust study design to investigate causality of therapeutic interventions and therefore they are positioned at the top of evidence hierarchies. However, RCTs are majorly powered for efficacy outcomes and *pivot* trials aim to produce the necessary evidence for drug approval. The methodological caveats of RCTs, in particular the fact that they are rarely designed to evaluate safety, made them susceptible to limitations that may hamper their ability to fully characterize drug-related harms[49]. Thus powered data of NOACs safety and tolerability from RCTs are required before massive post-marketing use of a new drug (a stage where no big 'real world' data is still available), as well as information from the national drug safety surveillance as a complement of safety evaluations from clinical trials.

Although oral anticoagulants are the few interventions that modulate the prognosis of atrial fibrillation, nothing was known about the impact of this prothrombotic disease of reference, in the society in terms of disability-adjusted life years (a measure of disease burden) and costs, and whether NOACs are cost-effective in the Portuguese society.

1.6. Objectives

This project aimed to fulfil some gaps of current available evidence about oral anticoagulation, particularly in atrial fibrillation, as well as the need to further improve the knowledge about NOACs (particularly regarding safety issues, as individual trials are unpowered for such evaluation) and their effectiveness and costs in Portugal.
In the research projects, whenever adequate, atrial fibrillation was considered the condition of reference of a prothrombotic disease requiring anticoagulation, although other conditions were also evaluated when it was methodological conceivable to increase the power and robustness of data.

In order to improve and to explore the limitations and areas of uncertainty about oral anticoagulants/NOACs, this dissertation provided research studies that approach all main fields of the population applications of clinical pharmacology, and whose objectives were:

Chapter II [Pharmacoepidemiology]: To evaluate and quantify the use of oral anticoagulants drugs in Portugal;
Chapter III [Comparative effectiveness/safety research]: To assess the overall safety of NOACs regarding bleeding, and non-bleeding adverse events and the impact in drug discontinuation;
Chapter IV [Pharmacovigilance]: To appraise the landscape of oral anticoagulants pharmacovigilance in Portugal;
Chapter V [Pharmacoeconomics]: To evaluate the socio-economic impact of atrial fibrillation (as a representative prothrombotic condition requiring anticoagulation) and NOACs in Portugal.

To achieve the proposed objectives, research projects were performed using the following methods: systematic reviews and meta-analyses, observational studies, burden of disease and cost of illness studies, and cost-effectiveness studies.

Chapter II

Pharmacoepidemiology of oral anticoagulants: trends in prescription patterns and drug use

Part of the contents of this chapter were published in:

- Caldeira D, Barra M, David C, Costa J, Ferreira JJ, Pinto FJ. The prevalence of oral anticoagulation in patients with atrial fibrillation in Portugal: Systematic review and meta-analysis of observational studies. ***Rev Port Cardiol.*** 2014;33:555-60.

- Caldeira D, Cruz I, Morgado G, Stuart B, Gomes C, Martins C, João I, Pereira H. Evaluation of time in therapeutic range in anticoagulated patients: a single-center, retrospective, observational study. ***BMC Res Notes.*** 2014;7:891.

2.1. The prevalence of Portuguese patients with atrial fibrillation treated with oral anticoagulation

BACKGROUND

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, with an estimated prevalence of 2.5% in the Portuguese population aged 40 and over according to the FAMA study. The prevalence increases with age, reaching 6.6% in the group aged 70 and over and 10.5% in those aged 80 and over [54].

In the FAMA study, a third of patients with AF were not aware that they had the condition. As AF can remain silent until complications occur [55,56], clinical screening is indicated for individuals aged 65 or over [57]. The main complications of AF are thromboembolic events, particularly stroke. For prevention of such events oral anticoagulation therapy is recommended in patients with thromboembolic risk factors [57].

The aim of this review was to estimate the prevalence of oral anticoagulant therapy in patients with AF in Portugal by means of a systematic review and meta-analysis of epidemiologic studies.

METHODS

Systematic review of observational studies performed in Portugal that enrolled patients with AF or atrial flutter and reported the proportion of anticoagulated patients were included. Studies on specific populations or on specific interventions such as AF ablation were excluded since inclusion of patients who are not representative of the general AF population would introduce bias.

MEDLINE, the Index of Portuguese Medical Journals and SIBUL (the Bibliographic Catalog of the Integrated Library System of the University of Lisbon) were searched. The search included review of the references lists of the studies and literature reviews found, but did not include abstracts of posters or oral communications at congresses.

The results of the individual and pooled studies were expressed in percentages (prevalence) and 95% confidence intervals (CI). Inverse-variance weighting was used to aggregate the

results of each study. As considerable heterogeneity between studies was expected, the random-effects model of DerSimonian and Laird was used by default [58].
In a separate analysis, estimates of prevalence were calculated as a function of the environment of the study (community or hospital).

RESULTS

Seven studies were included for analysis [54,59-64]. Their main characteristics are shown in Table 7.

Three studies were cross-sectional [54,59,63] and four were longitudinal (three retrospective cohort studies [60-62] and one prospective cohort study [64]). Three studies were conducted in the general community [54,59,62,63] and four in a hospital environment [60-62,64]. These studies enrolled a total of 891 AF patients eligible for oral anicoagulation. Sample size ranged between 21 and 261 individuals, most of them elderly (mean age varying between 77 and 85.5 years) and thus generally at high thromboembolic risk. Three studies included patients with significant valve disease or mechanical valves: in Jorge et al., 29% of the population had at least moderate valve disease or mechanical valves [62], in Ascenção et al., 20% had mitral stenosis [59], and in Dores et al., 6% of the population had valvular AF [61]. Thromboembolic risk stratification was performed using the $CHADS_2$and CHA_2DS_2-VASc scores and the risk categories proposed in the 2006 American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) guidelines[65]. Two studies did not report using any risk stratification tools [54,60].

The main source of possible bias was the lack of representativeness of the sample – some studies were performed exclusively in a hospital environment or analyzed patient subgroups.

The meta-analysis of the results reveals that the prevalence of oral anticoagulant therapy in Portuguese patients with AF is 40% (95% CI: 32–48%), higher in community-based (45%; 95% CI: 37–52%) than in hospital-based studies (36%; 95% CI: 24–48%), although this difference was without statistical significance (p=0.20). These results are presented in Figure 8.

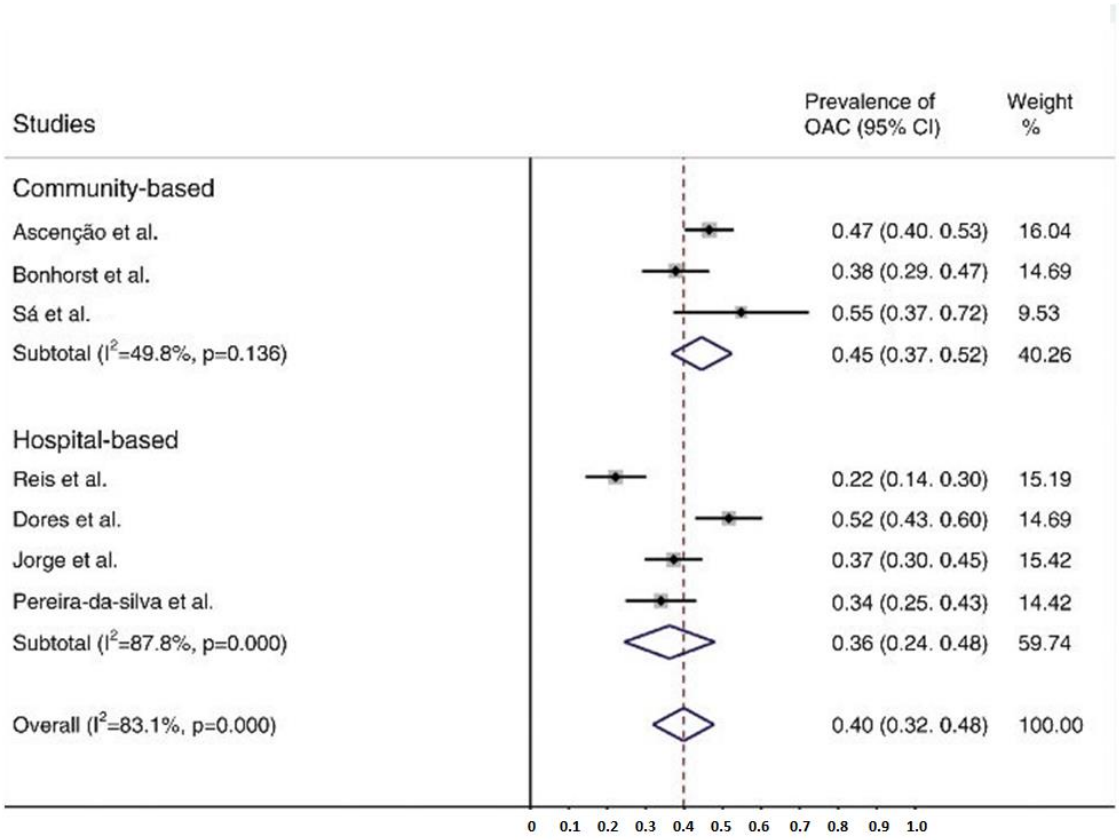

Figure 8: Forest plot evaluating the proportion of anticoagulated patients with atrial fibrillation. OAC: oral anticoagulation

Table 7: Main characteristics of studies included for evaluation of oral anticoagulants use in atrial fibrillation.

Study	Study design Environment	Study period	Patients eligible for OAC (n)	Mean/median age (years)	Indication for OAC
Ascenção et al.	Cross-sectional Community (general practitioner sentinel network)	June 2003–November 2003	243	84% >65	$CHADS_2$ ≥2, mitral stenosis or intracavitary thrombus
Reis et al.	Retrospective Hospital (HFF)	January 1996–December 2004 (data from 2004)	108	78.6	–
Bonhorst et al.	Cross-sectional Community	–	119 (previous diagnosis of AF)/69% total AF	77	–
Dores et al.	Retrospective Hospital (HSFX)	October 2006–October 2007	126	77	Moderate to high risk according to 2006 ACC/AHA/ESC guidelines
Jorge et al.	Retrospective Hospital (HUC)	December 2005–June 2007	161	80.9	$CHADS_2$ ≥2
Sá et al.	Cross-sectional Community (USF Saúde em Família, Maia)	2011	31	85.5	CHA_2DS_2-VASc ≥2
Pereira-Da-Silva et al.	Retrospective Hospital (CHLC)	April 2011–October 2011	103	79.6	CHA_2DS_2-VASc ≥2

ACC/AHA/ESC: American College of Cardiology/American Heart Association/European Society of Cardiology; AF: atrial fibrillation; CHLC: Centro Hospitalar Lisboa Central; HFF: Hospital Prof. Dr. Fenando Fonseca; HSFX: Hospital São Francisco Xavier; HUC: Hospitais da Universidade de Coimbra; OAC: oral anticoagulation; USF: Family Health Unit.

CONCLUSIONS

AF is an important public health issue, particularly in Portugal, since it is a risk factor for stroke, a significant cause of morbidity and mortality in this country [43]. There is solid evidence that oral anticoagulation reduces the risk of thromboembolic events. Use of vitamin K antagonists is associated with a significant reduction of 64% in relative risk for stroke.[35]

Despite the evidence and the recommendations concerning the reduction of thromboembolic risk in AF patients with this therapy, a significant proportion of the population at risk is not anticoagulated – about 40%. The level of oral anticoagulation prescription in these patients is an indication of the quality of health care, and there is an obvious need for change.

2.2. The quality of anticoagulation with VKA: a single-centre study

BACKGROUND

Vitamin K Antagonists (VKA) such as warfarin, acenocoumarol and phenpromcom are widely prescribed oral anticoagulant drugs. The main indications are atrial fibrillation (AF), valvular prosthesis, venous thromboembolism and intracavitary thrombus. These drugs' efficacy and safety depends on International Normalized Ratio (INR) monitoring. The absence of standard dosages of VKA turns imperative to perform serial INR tests and make dosages adjustments when the results are out of the range.

INR levels above and under pretended values are associated to increased risk of hemorrhagic and thromboembolic events, respectively [66,67]. Time in therapeutic range (TTR) is a measure of quality of anticoagulation and lower values are related to adverse events [68]. TTR knowledge is important to identify the current standard of anticoagulation care and establish new goals. Additionally, TTR is an important input to determine the cost-effectiveness of new oral anticoagulants [69].

The most comprehensive published data about TTR in Portuguese patients comes from RE-LY study. This trial included Portuguese patients and mean TTR for overall Portuguese centres was 61% [70,71].

TTR data retrieved from randomized controlled trials may overestimate those from real world[72]. In order to estimate TTR, a retrospectively review of patients charts from a single-center anticoagulation outpatient clinic was performed.

METHODS

Study design and setting

We conducted a retrospective cohort study of patients treated with vitamin K antagonists followed in Cardiology Anticoagulation Clinic a Portuguese single-centre from January 2011 to July 2013, in order to determine the TTR of the centre. We obtained Institutional Board and Ethics Committee approval for this study.

Participants, variables and statistical analysis

We identified all patients treated with vitamin K antagonists followed in Cardiology Anticoagulation Consultation. Patients' data were retrieved from Consultation database which contains the all INR records obtained in the visits. All patients were submitted to nurse led INR checking using CoaguCheck® XS system and follow-up was made according to INR value, and hospital protocol or physicians preferences.

For analysis, we included patients whose target INR was between 2.0 and 3.0 (patients with INR targets between 2.5 to 3.5, including patients with mechanical heart valves were excluded). To better characterize the quality of long-term anticoagulation all patients under 2 months of follow-up tests or <6 INR tests were excluded [73]. We have characterized the demographic and clinical characteristics of the population. For each patient we evaluated all available INR values to calculate the individual TTR according to the Rosendaal method [74].

Patients were clustered into subgroups according to the reason/indication for anticoagulation: non-valvular AF; valvular AF; venous thromboembolic disease; and others.

The primary outcome was the TTR, a continuous outcome. Secondary outcomes were: 1) TTR < 60%, a marker of poor quality in the control of INR [68,75]; 2) time under therapeutic range (INR < 2.0); 3) time over therapeutic range (INR > 3.0); 4) time with increased thrombotic risk (INR < 1.5); 5) time with increased hemorrhagic risk (INR > 4.5).

All analyses were conducted using SPSS software version 9.1. Statistical summary measures such as arithmetic mean and median were used to characterize the population. Standard deviation (SD) and interquartile range were used to evaluate data dispersion. Multivariate logistic regression analysis was performed to identify risk factors for TTR < 60%, at a significance level of 0.05. Chi-square test was performed for the comparison of dichotomic data across groups. One-way ANOVA was used to evaluate differences between TTR across indications (more than 2 groups).

RESULTS

We found 501 patients treated with VKA with target INRs between 2.0 and 3.0, with their INR recorded in the database between January 2011 and July 2013. About 377 patients had the minimum required follow-up/number of tests to meet the inclusion criteria.

The mean age was 71 years, and 59.4% of the patients were male. Most of the patients had non-valvular AF (72.4%), while valvular AF (19.1%) and venous thromboembolic disease (3.4%) were less common. The population's average CHA_2DS_2-VASc was 3.58.

Patients were followed for a mean period of 471 days, having performed on average 17 INR tests per year each patient. The average time between two tests was 25.4 days.

Table 8 shows the main characteristic of the population.

Table 8: Clinical characteristics of included patients.

Characteristics	Population (N = 377)
Age – years	
Mean (SD)	71.0 (10.4)
Median (IQR)	72.0 (66–79)
Female sex – no. (%)	153 (40.6)
Previous stroke or transient ischemic attack – no. (%)	56 (14.9)
Heart failure – no. (%)	160 (42.4)
Diabetes mellitus – no. (%)	101 (26.8)
Hypertension - no. (%)	253 (67.1)
Vascular Disease History – no. (%)	122 (32.4)
Indication for anticoagulation	
Non-valvular AF	273 (72.4)
Valvular AF	72 (19.1)
Venous thromboembolism	13 (3.4)
Others	19 (5.1)
CHA_2DS_2-VASc	
Mean (SD)	3.58 (1.62)
Median (IQR)	3 (2–5)

AF: Atrial Fibrillation; IQR: Interquartile Range; SD: Standard Deviation.

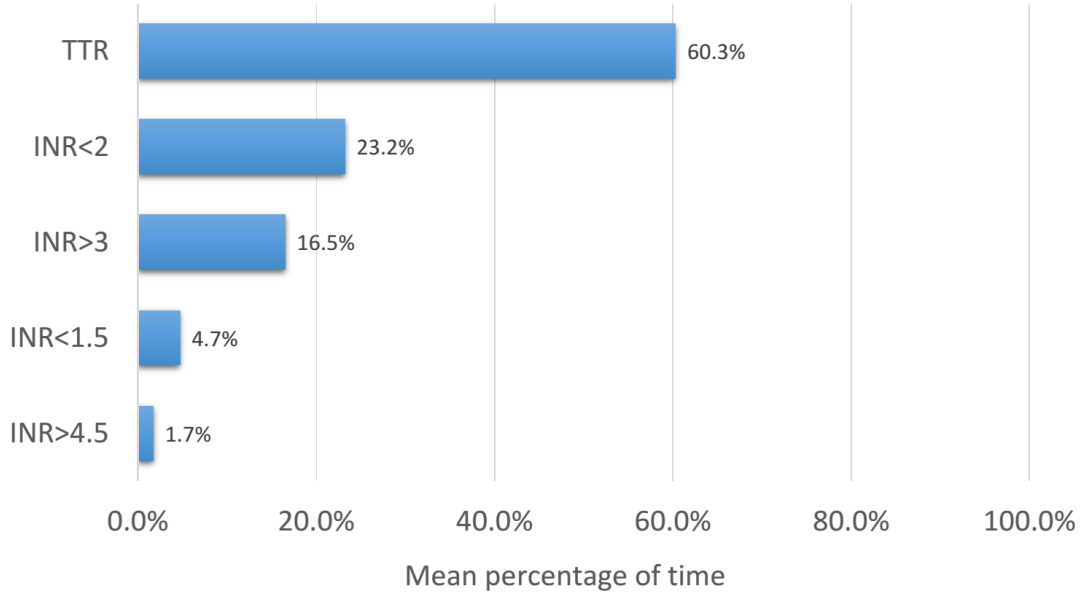

Figure 9: Percentage of time spent in each INR interval. TTR: Time in therapeutic range with INR 2.0-3.0.

The mean TTR was 60.3% (SD 19.3%) and the median 63% (interquartile range 47.9-74.8%). About 44.3% of the patients evaluated have a mean TTR < 60%, and are at increased risk of thrombotic and hemorrhagic events.

The female gender was the only characteristic that was significantly associated to poor anticoagulation control (TTR < 60%) in the multivariable regression analysis with an odds ratio 1.73 and 95% confidence interval 1.14-2.62 (p = 0.01).

The average percentage of time that patients remained above (INR > 3.0) and below the target INR (INR < 2.0) was 16.5% and 23.2%, respectively. Patients were at high risk of bleeding (INR > 4.5) 1.7% of the time, and at high thrombotic risk (INR < 1.5) 4.7% of the follow-up period. Figure 9 and Figure 10 illustrate these results.

Non-valvular AF was the most prevalent indication for anticoagulation. The mean CHA_2DS_2-VASc was 3.65 (SD 1.58). In this cluster of patients, the average TTR was 59.3% (SD 19.8%) and the median was 61.8% (interquartile range 47.4-73.7%). These patients were on average 23.4% of the time below therapeutic range (INR < 2.0), and 17.3% of the time over INR 3.0. The mean percentage of time with high thrombotic risk (INR < 1.5) was 5.3%, and 1.7% of the time patients were at high risk of bleeding.

There were no significant differences in average TTR between the different indications for VKA treatment (p = 0.18). The proportion of patients with low anticoagulation control also was not different across conditions (p = 0.53). Table 9 shows the mean TTR and the proportion of TTR < 60% according to the main indication for anticoagulation.

Table 9: Mean Time in Therapeutic Range (TTR) according to main indication for anticoagulation.

Population	Mean TTR (SD)	TTR < 60% (%)	Patients	Average follow-up (years)
Non-valvular AF	59.3% (19.7%)	128 (46.7%)	274	1.27
Valvular AF	64.0% (18.6%)	29 (40.3%)	72	1.44
Venous thromboembolism	54.6% (24.4%)	5 (38.5%)	13	1.18

AF: Atrial Fibrillation; SD: Standard Deviation; TTR: Time In Therapeutic Range.

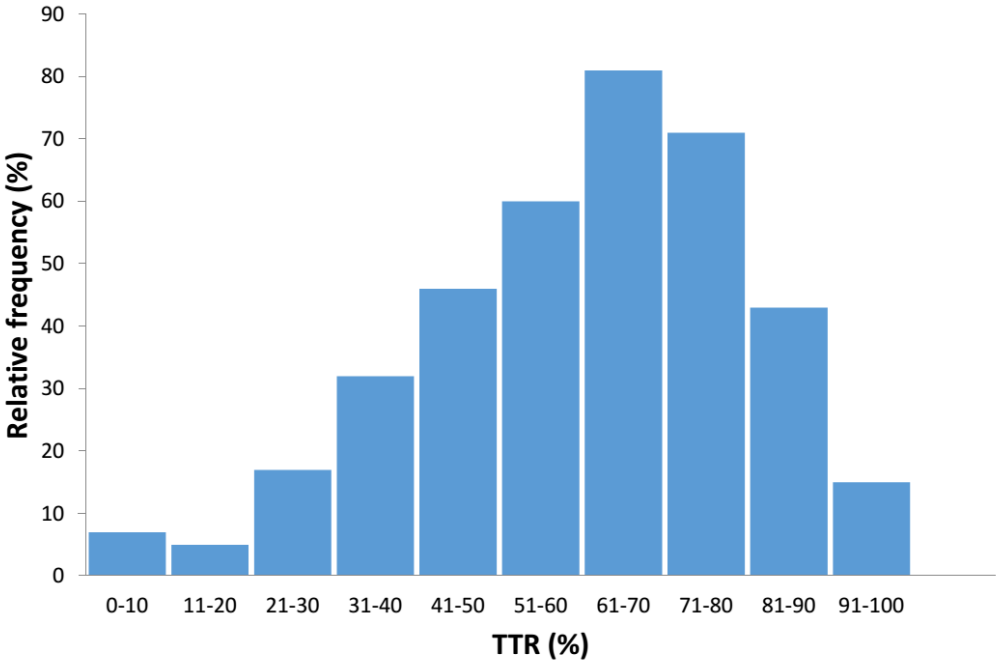

Figure 10: Histogram with relative frequencies of TTR values.

CONCLUSIONS

The Rosendaal TTR of this population of anticoagulated Portuguese patients was 60.3% during a mean follow-up of 1.3 years. Forty-four percent of this population had a TTR < 60%. When out of therapeutic range, patients were more commonly prone to prothrombotic risk due to the higher percentage of time with INR < 2.0. This means that an important proportion of patients are at increased risk of major adverse events [68,75,76].

Applying the data to those retrieved from randomized controlled trial, in centres with TTR of 60-61%, NOACs tend to be safer and/or more effective than VKA.

2.3. Prescription of anticoagulants in Portuguese outpatients: the pattern has changed towards NOACs

INTRODUCTION

Oral anticoagulation is the mainstay in the prevention or treatment of some prothrombotic conditions. In prevalent conditions such atrial fibrillation (AF), oral anticoagulation with VKA showed a stroke risk reduction superior to 50% .[77] Despite their demonstrated efficacy in clinical trials, the use of these drugs has consistently been reported as suboptimal as previously shown.[78]

Recently, new pharmacological options have been developed with the same therapeutic goals. The non-vitamin K antagonist oral anticoagulants (NOACs) are considered at least as effective as VKAs, with lower risk of intracranial hemorrhage,[79] without needing laboratory monitoring of international normalized ratio (INR). In Portugal, NOACs (dabigatran and rivaroxaban) were firstly widely used in 2010 with the reimbursement for the prevention of venous thromboembolism in patients undergoing hip or knee arthroplasty, and in 2011 the indication of NOACs was expanded to stroke prevention in non-valvular AF. In August 2014, three of these NOACs (apixaban, dabigatran and rivaroxaban) were approved for reimbursement under the National Health Service (NHS) for AF patients.

Overall oral anticoagulants prescription may be considered a marker of care in prothrombotic conditions, and the advantages of NOACs preclude an increase in the prescription of oral anticoagulants. Therefore, we aimed to evaluate the trends in the prescription of oral anticoagulants in Portugal, evaluating the role of NOACs and the reimbursement for AF in the prescriptions.

METHODS

We conducted an observational retrospective descriptive analysis of Portuguese landscape on the prescription of oral anticoagulants in the ambulatory care. In this study, drugs use/consumption was used as a proxy of prescription and we used these terms interchangeably.

Data sources and outcomes reported

Data from prescriptions were retrieved through the Portuguese National Authority of Medicines and Health Products (INFARMED) and IMS Health Portugal.

Data from Infarmed were used to analyse yearly data of the counting packs of oral anticoagulants sold from 2010 (year of reimbursement and wide use NOACs) to 2015, and the daily defined doses (DDD) as defined by the World Health Organization (WHO) from 2010 until the first trimester of 2016. Data from IMS Health were obtained through IMS dataview and reported all sells-in of oral anticoagulants in terms of counting packs and counting units (pills) in the last 4 years (from February 2012 until February 2016) by months.

Data management

We obtained data for the use of oral anticoagulants currently used in ambulatory care. These were grouped according to active substance in accordance with their WHO Anatomical Therapeutic Chemical (ATC) classification and afterwards according to their mechanism of action: VKA - B01AA; NOACs - B01AE07, B01AF01, B01AF02). Parenteral anticoagulants (e.g. heparins) or other oral anticoagulants not commercialized (e.g. edoxaban) were excluded.

As packs can have different presentations and units can have different doses, the daily defined doses were used to standardize the data. DDD is a statistical measure of drug consumption, defined by the WHO (http://www.whocc.no/atc_ddd_index/?code=B01A), and is the assumed average maintenance dose per day for a drug used for its main indication in adults. Atrial fibrillation is deemed to be the main indication for oral anticoagulation, and in 2016 the DDD for NOACs were updated in order to reflect this, with a 10 mg DDD for apixaban, 300 mg for dabigatran, and 20 mg for rivaroxaban.

Statistical analysis

A descriptive analysis was performed regarding the number of packs and counting units sold, and by DDD. Oral anticoagulants were globally evaluated as well as their both groups: VKA and NOACs. There were no demographic or clinical details about the patients that used the

drugs, the setting for the prescription. Linear regression parameters were estimated in order to retrieve the direction and significance of variations. Results were considered statistically significant if $p<0.05$. We also performed an analysis exclusive for prescriptions from August 2014 (date for reimbursement of all NOACs for non-valvular AF)

RESULTS

The prescription of oral anticoagulants in Portugal increased significantly (p for trend <0.05) in the last 6 years, according to the INFARMED data. The number of oral anticoagulant packs sold yearly increased from 579600 to 1405200 (relative increase of 242%) (Figure 11). In 2010 the mean number of DDD was 52121 and there was an increase of 2.3-fold over these 6 years (first trimester 2016 DDD: 120726).

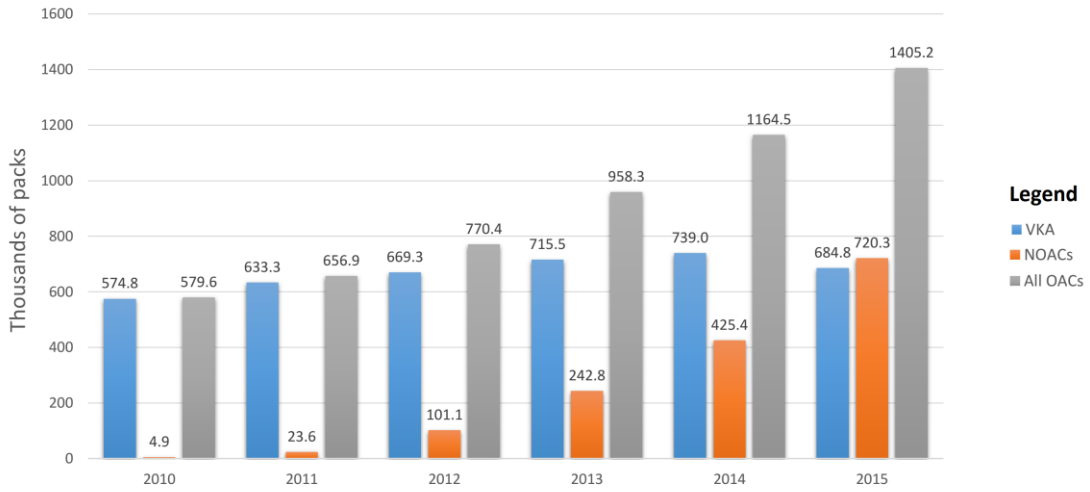

Figure 11: Yearly sold packs of oral anticoagulants. Source: INFARMED.

Until 2014 this increase was obtained through both VKA and NOACs, mostly by the latter. There was an increase of VKA (129% packs; 130% DDD) and NOACs (8682% packs; 13886% DDD) (Figure 11 and Figure 12).

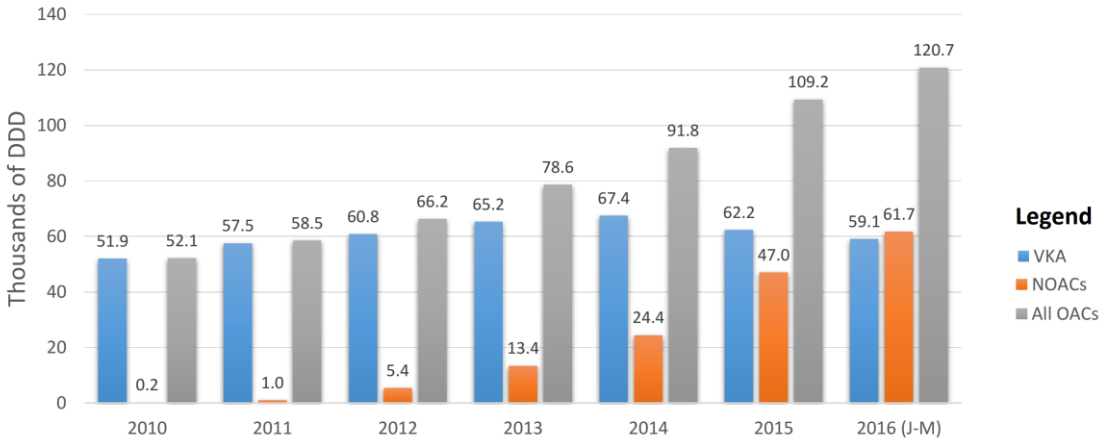

Figure 12: DDD of oral anticoagulants used in Portuguese outpatient setting. Source: INFARMED

In 2015, the prescription of oral anticoagulants remained with an increased trend compared with the previous years. There was though a small decrease in the prescription of VKA compared with 2014 (relative decrease 7.7%). In opposition to VKA, NOACs kept their prescription trends in a way that packs sold were greater than VKA since 2015 (51.3% of the market of oral anticoagulants in 2015, and 58.4% in the first trimester of 2016). Considering DDD, only data from the first trimester of 2016 showed preponderance of NOACs (Table 10).

Table 10: NOACs market share from 2010 to 2016*.

Market share of NOACs (%)	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016***
Packs	0.8%	3.6%	13.1%	25.3%	36.5%	51.3%	58.4%
DDD	0.3%	1.7%	8.2%	17.0%	26.6%	43.0%	51.1%

DDD: Defined daily dose; NOACs (Non-vitamin K antagonist oral anticoagulants).
* January to March 2016. Source: INFARMED.

The analysis of data provided by the IMS Health was overall similar to that provided by the INFARMED. Linear regression of the data of the last 4 years (February 2012 to February 2016) showed that the prescription of anticoagulants remains increasing linearly, mostly due to NOACs, while VKA prescription did not change significantly (p value for trend 0.053).

NOACs dominance in the market of oral anticoagulants in terms of packs and counting units was firstly established in May 2015 and remains linearly increasing (Figure 13).

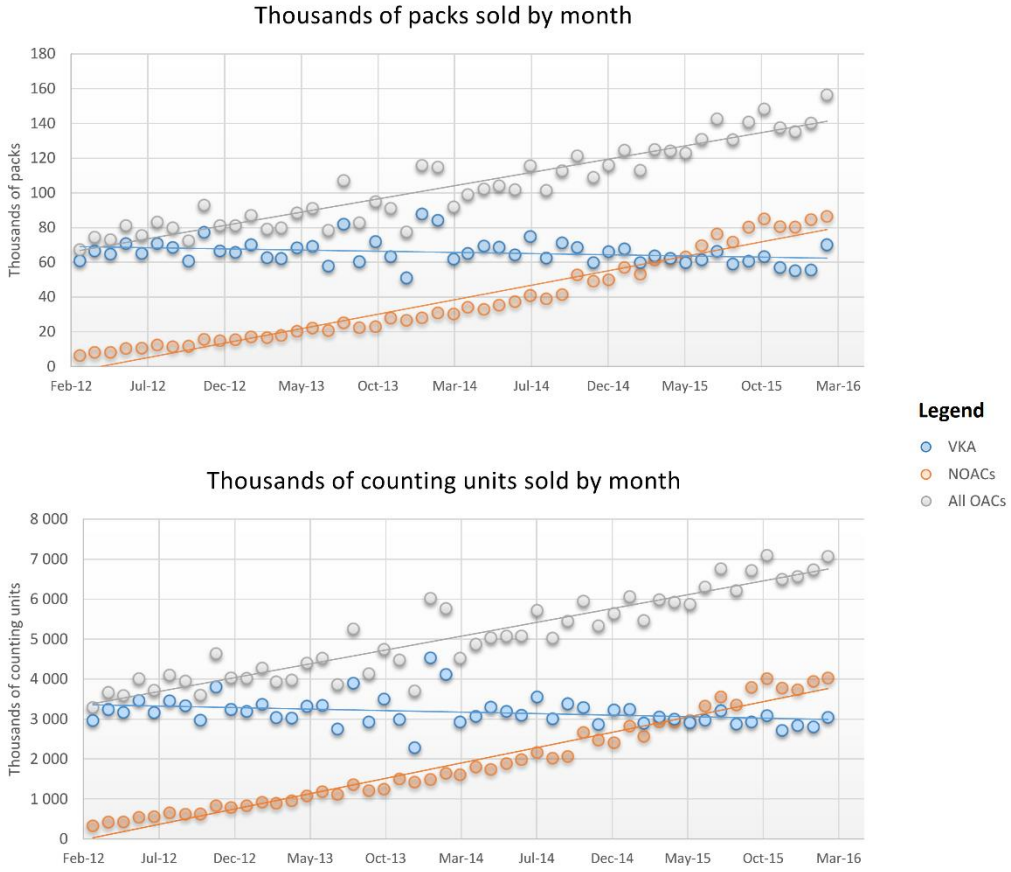

Figure 13: Packs and counting units sold by month. Source: IMS Health. Dots are the monthly estimates and the solid lines are the linear regression lines

The impact of reimbursement for atrial fibrillation

As all NOACs were reimbursed for non-valvular AF in August 2014. A linear regression analysis was performed in order to evaluate whether reimbursement changed the pattern of prescription. The analysis showed that the prescriptions of OACs and NOACs after the reimbursement were still increasing (p-value for trend <0.001), while VKA showed a tendency to decrease (p=0.06). When the rates of growth of oral anticoagulants use (slope analysis) were compared before and after August 2014, the data was significant a greater growth of OACs prescription (p=0.005), due to a further increase in the NOACs prescription (p<0.001). The prescription of VKA was not significantly different from the period before August 2014 (p=0.12) and there was a trend towards a decrease in the prescription of VKA.

CONCLUSIONS

The Portuguese national outpatient prescription data showed that the prescription of oral anticoagulants is increasing, mostly due to NOACs, while VKA prescriptions were overall kept overtime.

Between 2010 and the first trimester of 2016, the number of packs sold increased significantly. Confounding factors such as pack sizes, doses and posologies, were adjusted through the prescribed DDD of oral anticoagulants which increased 2.3-fold along the referred timeframe.

In August 2014, all NOACs were reimbursed for atrial fibrillation. The rate prescriptions growth increased significantly after this period, while VKA prescriptions look unchanged, but a negative trend was observed. Due to the non-significant variation of VKA, it is plausible that only a small proportion of patient changed from VKA to NOACs. in the oral anticoagulants.

Although not detailed nor conclusive, data are suggestive that the increase of NOACs prescription comes mainly from new prescriptions of oral anticoagulants instead of changes in oral anticoagulants.

2.4. Chapter discussion and conclusions

Until recently, the proportion of patients eligible for receiving oral anticoagulant treatment was unacceptably low. The presented systematic review with meta-analysis estimated that only 40% of the patients were treated accordingly. The international scenario is very heterogeneous. Only the Italian ISAF study showed a proportion similar to the presented study (ISAF 46% vs. Caldeira et al. 40%) [80]. Other studies such as the international prospective GARFIELD registry (62%) [81], the German primary care ATRIUM registry (75%) [82], and the international (seven European countries) PREFER in AF registry (85%) [83] showed higher proportions of anticoagulated patients.

Another flaw related to the anticoagulant treatment, particularly in VKA, relies on the absence of adequate control of the INR. Until recently, it was unknown how Portuguese patients were controlled in terms of Time in Therapeutic Range (TTR), a standardized method to benchmark and compare centres and countries.
In this chapter are published the results of the first Portuguese study, outside the clinical trials setting, which characterized the Time in Therapeutic Range through the Rosendaal method in a large number of patients. This retrospective study appraised more than 350 patients and their INRs for a mean of 1.3 years. The mean TTR of the sample was 60.3%, the median was 63%, and 44% of these patients had a TTR<60%. As a title of example, an effective stroke risk reduction is only obtained when TTR>65-70%[15,84]. The results obtained in this study were similar to those seen in Portuguese patients included in the RE-LY trial (TTR 61%), and were in accordance to those reported in the literature[71,85].

There were, then, 2 major problems identified: the low rate of oral anticoagulants prescription; and in those who were anticoagulated, the overall control of INR was suboptimal and a significant proportion of patients had a TTR<60%.

These unmet medical needs were fulfilled by NOACs as seen in the Portuguese national outpatient prescription data. Prescription of oral anticoagulants is increasing, mostly due to NOACs, while VKA prescriptions were overall kept overtime. The increase in the

prescription of oral anticoagulants is also explained by the reimbursement of NOACs, which are at least as efficacious as VKA,[86] and more convenient.

Besides the absolute increase of oral anticoagulants prescription, NOACs also bring the advantage of anticoagulation control due to the predictability of the anticoagulant effect. Applying the presented data to those retrieved from randomized controlled trial, in centres with TTR of 61%, NOACs tend to be safer and/or more effective than VKA. In RE-LY, all dosages (110 mg and 150 mg bid) had a significant lower risk of intracranial bleeding, with a similar risk major bleeding, while in the prevention of thromboembolic events only the dosage of 150 mg showed a significant risk reduction compared to warfarin. The efficacy of rivaroxaban was not statistically different from warfarin but there was a trend towards rivaroxaban in the prevention of thromboembolic complications (HR 0.70; IC95% 0.48-1.03). Apixaban was safer in terms of major bleeding with an efficacy likely to be better than warfarin (HR 0.73; IC95% 0.53-1.00).

The prescription of oral anticoagulants was low and treated patients did not have an adequate control (low TTR). The paradigm in Portugal is changing towards an improvement of oral anticoagulants prescription, mostly due to NOACs, that do not have the previously mentioned control issues.

Between 2010, when dabigatran (the first NOAC) was firstly marketed, and first trimester of 2016, the number of packs sold increased significantly. Confounding factors such as pack sizes, doses and posologies, were adjusted through the prescribed DDD of oral anticoagulants which increased 2.3-fold along the referred timeframe. Interestingly, the DDD analysis shows that in 2016, the mean daily sells of oral anticoagulants correspond to 120000 individual doses. Interestingly the extrapolation the AF prevalence of 2.5% in individuals with more than 40 years-old to the overall Portuguese population suggests that in Portugal there are about 121000 patients with AF.

Limitations

In the systematic review and meta-analysis evaluating the proportion of AF patients treated with oral anticoagulants, it should be considered that clinical heterogeneity from the inclusion of studies with different populations, different settings (hospital vs. community) which used different methods to prescribe the anticoagulation to the thromboembolic risk (use of

$CHADS_2$ or CHA_2DS_2-VASc) must be acknowledged as limitation. The expected statistical heterogeneity also limits the conclusions.

The other two studies of this chapter (TTR evaluation and prescription of oral anticoagulants in Portuguese outpatients) had a retrospective design.

The TTR evaluation was a retrospective cohort of patients anticoagulated with VKA followed in the Cardiology Anticoagulation Consultation of a single-centre. The data presented does not account for INR values registered in other facilities, such as in the emergency room or during hospitalizations. These reasons may limit the conclusions of this study.
We did not focus on other patients with very high thrombotic risk such as those carrying mechanical heart valves (because INR target is 2.5-3.5). So the data here presented cannot be extrapolated to such subgroup.

Its known that the use of oral anticoagulants is not disease-specific, i.e. these drugs are not indicated exclusively for patients with atrial fibrillation (the reference condition).
However, it is estimated that AF corresponds to the largest proportion of patients treated with these drugs. It is also possible that prescription for venous thromboembolism treatment (VTE), or VTE prevention in elective hip or knee arthroplasty could have contributed for the increase of the prescriptions, but these are mostly candidates for a limited anticoagulation period. Furthermore, VTE preventions doses are inferior to the DDD actually considered, which limits the impact of these indications in the cumulative data of all these years. AF patients are candidates for life-long anticoagulation, unless they have a low thromboembolic risk or formal contra-indication.

CONCLUSIONS

It was estimated that in Portugal about 60% of patients with AF were not treated with oral anticoagulants. This single-centre retrospective study showed that oral anticoagulation with VKA has a suboptimal control with a mean TTR of 61%.
Since the introduction of NOACs in the Portuguese market, the number of pack and DDD of oral anticoagulants prescribed significantly increased, due to NOACs. Currently the NOACs, as a pharmacological group, have most of the market share of oral anticoagulants.

Chapter III

Comparative safety and tolerability of oral anticoagulants

Part of the contents of this chapter were published in:

- Caldeira D, Costa J, Fernandes RM, Pinto FJ, Ferreira JJ. Performance of the HAS-BLED high bleeding-risk category, compared to ATRIA and HEMORR2HAGES in patients with atrial fibrillation: a systematic review and meta-analysis. ***J Interv Card Electrophysiol.*** 2014;40:277-84.

- Caldeira D, Rodrigues FB, Barra M, Santos AT, de Abreu D, Gonçalves N, Pinto FJ, Ferreira JJ, Costa J. Non-vitamin K antagonist oral anticoagulants and major bleeding-related fatality in patients with atrial fibrillation and venous thromboembolism: a systematic review and meta-analysis. ***Heart.*** 2015;101:1204-11.

- Caldeira D, Barra M, Ferreira A, Rocha A, Augusto A, Pinto FJ, Costa J, Ferreira JJ. Systematic review with meta-analysis: the risk of major gastrointestinal bleeding with non-vitamin K antagonist oral anticoagulants. ***Aliment Pharmacol Ther.*** 2015; 42:1239-49

- Caldeira D, Barra M, Pinto FJ, Ferreira JJ, Costa J. Intracranial hemorrhage risk with the new oral anticoagulants: a systematic review and meta-analysis. ***J Neurol.*** 2015 Mar;262:516-22.

- Caldeira D, Canastro M, Barra M, Ferreira A, Costa J, Pinto FJ, Ferreira JJ. Risk of Substantial Intraocular Bleeding With Novel Oral Anticoagulants: Systematic Review and Meta-analysis. ***JAMA Ophthalmol.*** 2015;133:834-9.

- Caldeira D, Barra M, Gonçalves N, Pinto FJ, Ferreira JJ, Costa J. Pericardial bleeding risk with non-vitamin K oral anticoagulants: a meta-analysis. ***Int J Cardiol.*** 2015;182:187-8.

- Caldeira D, Barra M, Santos AT, de Abreu D, Pinto FJ, Ferreira JJ, Costa J. Risk of drug-induced liver injury with the new oral anticoagulants: systematic review and meta-analysis. ***Heart.*** 2014;100:550-6.

- Caldeira D, Gonçalves N, Pinto FJ, Costa J, Ferreira JJ. Risk of renal failure with the non-vitamin K antagonist oral anticoagulants: systematic review and meta-analysis. ***Pharmacoepidemiol Drug Saf.*** 2015;24:757-64.

- Caldeira D, Costa J, Pinto FJ, Ferreira JJ. The risk of infection with new oral anticoagulants: a meta-analysis. ***Int J Cardiol.*** 2014;172:267-8.

- Caldeira D, Barra M, Santos AT, de Abreu D, Costa J, Ferreira JJ. Risk of insomnia with non-vitamin K oral anticoagulants: systematic review and meta-analysis. ***Sleep Breath.*** 2015;19:1043-9.

- Caldeira D, Gonçalves N, Ferreira JJ, Pinto FJ, Costa J. Tolerability and Acceptability of Non-Vitamin K Antagonist Oral Anticoagulants in Atrial Fibrillation: Systematic Review and Meta-Analysis. ***Am J Cardiovasc Drugs.*** 2015;15:259-65.

3.1. Methodology: systematic review and meta-analysis

The systematic reviews presented in this dissertation followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[87].

Eligibility criteria

The eligibility criteria must comply with the focus/question of the review. In order to endeavor the objective nature of the systematic reviews, all of them followed the PICOS acronym to establish the question.

PICOS acronym is the guide to define the **P**opulation/patients, the **I**ntervention to be studied, the **C**omparisons/comparators, the **O**utcomes evaluated, and the **S**tudy designs that more reliably answer to the question of the review. The approach to each one of these points is detailed ahead.

***P**opulation/patients*

All studies had to include patients with prothrombotic conditions requiring anticoagulant drugs.

For bleeding risk evaluation, the length of therapy / follow-up period are important factors[88]. Although many major bleeding events occur in the first weeks of anticoagulant treatment it is possible that the process may be related to previous established structural prone areas. Following the patients for longer periods captures more events and helps to establish more robustly the safety profile. AF usually requires life-long anticoagulation and VTE often requires anticoagulation for a period of at least 3 months, with the duration based on the benefits and risk of therapy. Therefore, bleeding risk appraisal was performed in AF or VTE patients requiring oral anticoagulation with NOACs or VKA (with or without an initial stage with low-molecular-weight heparin) (Table 11).

For non-bleeding adverse events assessment, other conditions (and comparators) rather than AF and VTE were allowed when the baseline conditions and comparisons were not expected

a priori to influence the outcome (e.g. drug-induced liver injury), in order to increase the power of the analysis (Table 11).

For assessment of tolerability and acceptability of NOACs, only AF patients were included as trials in this condition are longer and capture more reliably differences in the adherence to treatment along time (Table 11). Tolerability represents the degree to which overt adverse effect can be tolerated by the subject. In other words, evaluates the seriousness of adverse events and the potential impact on drug discontinuation (acceptability). While VTE treatment or prevention may require only temporary anticoagulant treatment[89,90], stroke prevention in AF demands life-long treatment. Therefore, the potential clinical benefits of anticoagulants are only outweighed if drug-related harms and their adherence profile are at least similar to their comparators in trials that are long enough to reflect potential differences in tolerability and acceptability/drug discontinuation.
Thus, tolerability and acceptability are essential components of safety.

***I**ntervention and **C**omparators*

All RCTs evaluating NOACs (oral IIa inhibitors: dabigatran; oral Xa inhibitors: apixaban, edoxaban, or rivaroxaban) were included.
Only phase III RCTs were considered to avoid bias in risk estimation due to statistical effects of rare events and the impact of small size underpowered studies on meta-analysis results[91-94]. Furthermore, we were interested in determining the risk associated with the NOACs doses transposed to phase III trials. Therefore, phase II RCTs (such as the previously mentioned RE-ALIGN[40]) were excluded.

Regarding bleeding risk, tolerability and acceptability evaluations, NOACs were compared to VKA (with or without initial treatment with LMWH) (Table 11).

In the assessment non-bleeding adverse events, NOACs were allowed to be compared with any control (VKA, LMWH, acetylsalicylic acid, placebo, mechanical thromboprophylaxis or placebo) (Table 11).

Table 11: Conditions and controls evaluated with NOACs phase III trials according to the outcome of interest.

Outcomes	Conditions	Controls
Bleeding adverse events	AF and VTE	VKA (with or without LMWH)
Non-bleeding adverse events	All (AF, VTE, VTE prevention, ACS…)	VKA, LMWH, ASA, Placebo, Mechanical VTE prevention
Tolerability and acceptability	AF	VKA

ACS: Acute coronary syndrome; AF: Atrial fibrillation; ASA: Acetylsalicylic acid; LMWH: Low-molecular-weight heparin; VKA: Vitamin K Antagonists; VTE: Venous thromboembolism.

Outcomes

Bleeding risk assessment followed the standardized major bleeding criteria for clinical investigations among non-surgical patients established by the International Society of Thrombosis and Haemostasis (ISTH)95. Accordingly, we have evaluated the following types of major bleeding:

- Major bleeding and bleeding related mortality, which included the evaluation of overall major bleedings (according to the ISTH definition), fatal bleedings, Major bleeding case-fatality rate (defined as the ratio between fatal bleeding and major bleeding events), and all-cause mortality in major bleeding survivors;
- Major gastrointestinal bleeding, which is the most frequent site of bleeding in anticoagulated patients;
- Intracranial hemorrhage, the bleeding site that mostly results into death or severe disability;
- Other major bleeding sites that can impair quality of life such as intraocular bleeding, or other rare but potentially lethal such as pericardial bleeding.

The evaluated non-bleeding adverse events were related to the potential pharmacokinetics of the anticoagulants, or to unexpected findings in trials, observational studies, or in anecdotal case report letters. The following outcomes were assessed:

- Drug-induced liver injury (DILI), defined as increases in serum levels of transaminases above three times the upper limit of normal (ULN) and total bilirubin above two times the ULN. According to Hy's law, the outcome defined above is the most specific predictor of potential severe hepatotoxicity[96]. Other

hepatic outcomes studied were incidence of transaminases elevation >3x ULN, and incidence of bilirubin elevation >2x ULN.

- Renal failure was defined primarily as events requiring dialysis or reported renal failure as treatment-emergent serious adverse event by investigators. Other outcome definitions were also explored.
- Insomnia was evaluated as an adverse event as reported by trials' investigators.
- Overall infections, post-surgery infection and urinary tract infection adverse events.

The overall tolerability and acceptability were evaluated in patients with AF compared with VKA.

- Tolerability was indirectly evaluated by determining the incidence of any serious adverse event (SAE[1]), as reported by investigators and/or adjudicated by committees. Whenever possible, treatment-emergent SAEs were retrieved.
- Acceptability[97] was split in drug-related (also associated to the tolerability profile) and patient-related treatment discontinuation. Discontinuations due to adverse events were considered to be drug-related, and discontinuations due to patients' own decisions (consent withdrawal and treatment discontinuation) were considered to be patient-related.

***S**tudy design*

Randomized controlled trials have the best methodology to properly evaluate the comparative efficacy and/or safety of two or more therapeutic interventions. In the systematic reviews here presented only phase III RCTs were included. The reasons for this option is related to the small studies bias risk, rare events and NOACs doses.

Information sources and search method

Records of potentially eligible studies were identified through an electronic search of bibliographic databases, usually MEDLINE (using OVID interface), CENTRAL at Cochrane Library, and Web of Science. Other databases could be searched according to the purposes of the systematic review. No language restrictions were applied. Systematic reviews and meta-analyses evaluating the topic, as well as reference lists of reports of potential eligible studies were comprehensively searched.

[1] Fatal or life-threatening events, disabilities, or situations that require or prolong hospitalizations.

The search strategy was exhaustively discussed and determined with accordance with methodologists in order to pursue the balance of a highly sensitive search with an adequate specificity. Full methods for search are detailed in the Appendix and are explained in the full text of each published article.

Study selection and data collection process

Titles and abstract of records obtained in the search process were screened by two investigators. Doubts and disagreements were solved by consensus or. Whenever needed a third element was consulted. Selected studies were assessed in full-text to determine its appropriateness for inclusion. Data from included studies were independently extracted by two authors to an electronic form. Retrieved data items were: study design, year of publication, patients' characteristics, and drugs used, studies' outcomes, data of required outcomes and estimates adjustments.

Studies included in the review are briefly characterized in the Appendix.

Data analysis

RevMan sotware (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to derive forest plot showing the results of individual studies and pooled analysis.

All the outcomes were summarized as dichotomous data.

The estimate measures were reported as Risk Ratio (RR) or Odds Ratio (OR) with their 95% confidence intervals (95%CI). Relative risk measures, such RR/OR (in opposition to risk difference which is an absolute risk measure) are more similar across studies with different designs, populations and lengths of follow-up compared to absolute measures, such as risk difference [98].

Random effects model was used independently of the existence ($I^2 \geq 50\%$) or not of substantial heterogeneity between studies' results because included studies had different characteristics. Furthermore, this method provides more conservative estimates.

Heterogeneity measured as the percentage of total variation between studies due to heterogeneity was assessed through the I^2 tests[99].

When significant differences were found an absolute risk measure was determined: Number Needed to Treat (NNT) or Harm (NNH), or the number of events avoided/caused per 1000 treated-patients.

3.2. Bleeding adverse events

Bleeding events bring concerns for patients taking anticoagulant drugs and for healthcare professionals who support them. The annual major bleeding rates for patients treated with the classical Vitamin K Antagonists (VKA) ranges from 1.3% to 3.4% [100,101]. These events usually require long hospitalizations and relevant resource use[102]. Major bleedings usually require transitory interruption of anticoagulant drugs. Their unavoidable suspension in patients with high thrombotic risk may be fatal. Bleedings events are then associated with significantly increased risk of mortality [103], due to the direct effects of the bleeding or due to thrombotic events.

Many bleeding risk prediction models have been developed in order to detect these clinical relevant events in patients with atrial fibrillation (Figure 14), mainly based in patients naïve regarding anticoagulant drugs or treated with VKA.

HAS-BLED is a simple tool and seems to perform well compared to the other in terms of the sensitivity of the high-risk category. However, its sensitivity is about 50% in both AF and VTE patients [104]. This area requires, therefore, further improvements and faces new challenges with NOACs arrival.

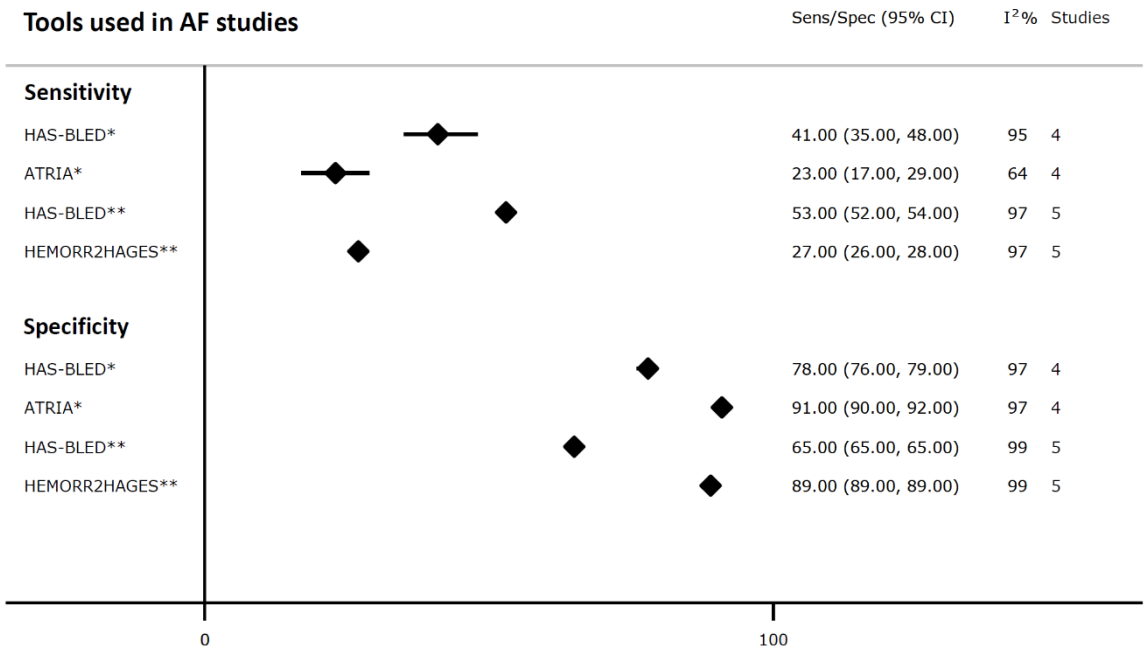

Figure 14: Pooled sensitivity and specificity of tools used for major bleeding risk prediction in AF. *Data from 4 studies evaluating HAS-BLED and ATRIA in the same population. **Data from 5 studies evaluating HAS-BLED and HEMORR2HAGES in the same population. Adapted from Caldeira et al. J Interv Card Electrophysiol 2014.

Independently of all characteristics considered in the mentioned bleeding-risk tools, the length of therapy as well as the follow-up period are important factors to evaluate these adverse events[88]. Although many major bleedings occur in the first weeks of anticoagulant treatment it is possible that the process may be related to previous established structural prone areas, while following patient for longer periods captures more events and helps to establish more robust safety profile of studied drugs.

Therefore, for bleeding risk evaluation, NOACs were compared with VKA in patients requiring medium or long-term anticoagulation. Pragmatically, this includes all trials evaluating patients with non-valvular AF and VTE. As occurs in the clinical practice VKA was complemented with a low-molecular-weight heparin in the initial phase, but it was not detrimental for the analysis.

The definition of major bleeding has been controversially discussed because each condition has its own peculiarities. In cardiovascular trials have used many definitions, as defined by the Thrombolysis in Myocardial Infarction (TIMI) or the The Global Use of Strategies to Open Occluded Arteries (GUSTO) [105].

In 2005, the International Society of Thrombosis and Haemostasis (ISTH) established a standardized major bleeding criteria for clinical investigations among non-surgical patients [95] (Table 12). Major bleeding was here defined according to the ISTH definition.

Table 12: ISTH Major Bleeding definition: (required to have at least one of the following criteria)

Fatal bleeding
Symptomatic bleeding in a critical area or organ Intracranial Intraspinal Intraocular Retroperitoneal Intra-articular Pericardial Intramuscular with compartimental syndrome
Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells

3.2.1. Major bleeding, fatal bleeding events and major bleeding-related mortality

BACKGROUND

The profile of NOACs seems to exceed other antithrombotic drugs, namely vitamin K antagonists (VKA), in the predictability of the dose-response relation, lack of coagulation monitoring and dose adjustments needs, and fast onset of action[19]. However, the inexistence of an antidote for NOACs for emergent hemorrhagic events is considered by many as one of the main drawbacks of this group of drugs and argues against their routine use [106-108].

To evaluate the risk of hemorrhagic-related fatalities associated with NOACs in comparison with vitamin K antagonists (VKA) a systematic review with meta-analysis was performed. Major bleeding and fatality cases, directly or indirectly related to the major bleeding events, reported in randomized controlled trials (RCTs) of patients requiring medium or long-term anticoagulation were analysed.

METHODS

This was a systematic review and meta-analysis of randomized controlled trials (full methodology detailed the published version of the article and briefly explained in the Section 3.1) comparing NOACs, against VKA or sequential treatment of LMWH and VKA in patients with atrial fibrillation (AF) or venous thromboembolism (VTE).

The objective was to evaluate the risk of major bleeding, and overall mortality directly or indirectly associated with major bleeding events. Therefore, the main outcomes were: incidence of major bleeding, fatal bleeding; major bleeding case-fatality rate; and all-cause mortality in major bleeding survivors.

Fatal bleeding events were defined as events in which the cause of death was a direct consequence of a major bleeding event. Major bleeding case-fatality rate was defined as the ratio between fatal bleeding and major bleeding events. In patients who survived to a major bleeding event, all-cause mortality was also evaluated.

RESULTS

Twelve studies[70,109-120] were included for analysis: 5 studies on AF[70,109-112] and 7 studies on VTE[113-120].

A total of 102790 patients were enrolled (71.0% with AF) with a mean age of 71 years for AF patients and 56 years for VTE patients. Mean follow-up period ranged from 1 to 2.8 years for AF trials, and most of VTE patients had a 6 months' follow-up.

Major bleeding risk analysis

NOACs were significantly associated to a decreased risk of overall major bleeding both in AF and VTE. With exception of rivaroxaban in ROCKET AF[110], all trials showed at least a trend towards major bleeding risk reduction.

In AF trials, NOACs were associated with a 20% risk reduction in major bleeding (RR 0.80, 95%CI 0.66-0.96). The NNT to avoid one major bleeding in AF patients was 82 (95%CI: 48 to 410), which means that NOACs are likely to avoid 12 major bleedings (95%CI: 2.4 to 20.8) *per* 1000 treated patients.

In VTE studies, a 39% major bleeding risk reduction was noticed (RR 0.61, 95%CI 0.46-0.80). Compared with VKA, there was a significant 28% major bleeding risk reduction with NOACs (RR 0.72, 95% 0.61 to 0.85) in these patients. The NNT to avoid one major bleeding in VTE patients was 148 (95%CI: 107.1 to 289.1). NOACs are therefore likely to avoid 7 major bleedings (95%CI: 3.5 to 9.3) *per* 1000 treated VTE patients.

Overall, NOACs showed to reduce significantly the risk of major bleeding compared to VKA. There was a significant 28% of major bleeding risk reduction (RR 0.72, 95%CI: 0.61 to 0.84; I^2=77%). However, the analysis is limited by substantial heterogeneity which may be related to the characteristics of individual NOACs and populations. Overall, the NNT to avoid one major bleeding was 77 (95%CI: 55.2 to 134.4). The number of major bleeding events avoided per 1000 patients treated with NOACs was 13 (95%CI: 7.4 to 18.1).

Figure 15 shows the forest plots of the analyses.

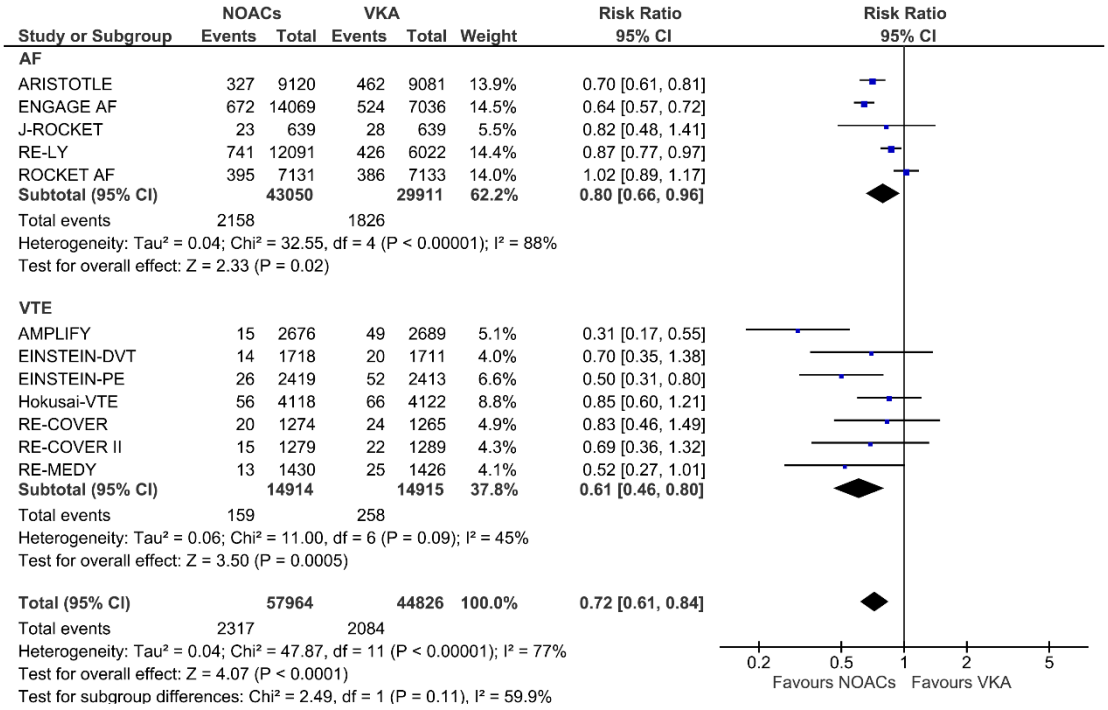

Figure 15: Forest plot of major bleeding risk associated with NOACs compared to VKA.

Fatal bleeding risk analysis

In AF patients, NOACs were associated with a 47% risk reduction in the risk of fatal bleeding (RR 0.53, 95%CI: 0.42 to 0.68; I^2=0%). The NNT to prevent one fatal major bleeding was 419 (95%CI: 339.2 to 615.0), and the number of fatal bleeding events avoided per 1000 patients treated with NOACs was 2 (95%CI: 1.6 to 2.9) in a period of 1 to 2.8 years.

In VTE patients, NOACs were also associated with a significant 64% risk reduction in the risk of fatal bleeding (RR 0.36; 95%CI: 0.16 to 0.81; I^2=0%). The number of fatal bleeding events avoided per 1000 patients treated with NOACs was 1 (95%CI: 0.3 to 1.3), and the NNT was 1013 (95%CI: 772.0 to 3413.0) for an average period of 6 months.

Overall, NOACs showed a significant risk reduction in fatal bleeding risk with a RR of 0.52 (95%CI: 0.41 to 0.65; I^2=0%). NNT for global analysis was 533 (95%CI: 434.2 to 731.9), and events spared for each 1000 patients treated with NOAC were 2 (95%CI: 1.4 to 2.3).

Figure 16 shows the forest plot for this outcome.

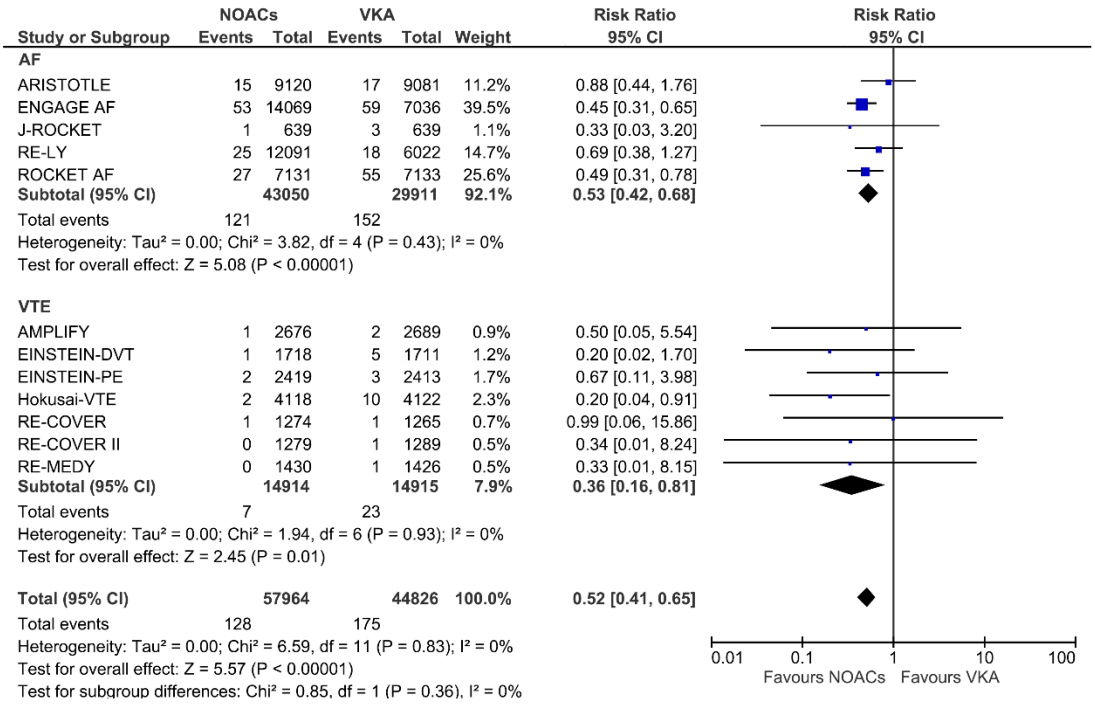

Figure 16: Forest plot of fatal bleeding risk associated with NOACs compared to VKA.

Major bleeding case-fatality rate analysis

Case-fatality rate was lower for AF patients treated with NOACs. Pooled analysis showed a significant 30% risk reduction (RR 0.70, 95%CI: 0.51 to 0.95; I^2=33%) (Figure 17). For each 40 patients (95%CI: 24 to 240) experiencing a major bleeding event with NOACs, one bleeding fatality is avoided compared to VKA. Regarding VTE, NOACs did not significantly reduced major bleeding case-fatality rate (RR 0.57; 95%CI: 0.26 to 1.27; I^2=0%) (Figure 17). Overall, considering all trials, NOACs were associated with a 33% risk reduction of major bleeding case-fatality rate (RR 0.67, 95%CI: 0.53 to 0.84; I^2=0%). Globally, one fatal bleeding was avoided for each 36 patients (95%CI: 25.3 to 74.4) experiencing a major bleeding event with NOACs compared to VKA.

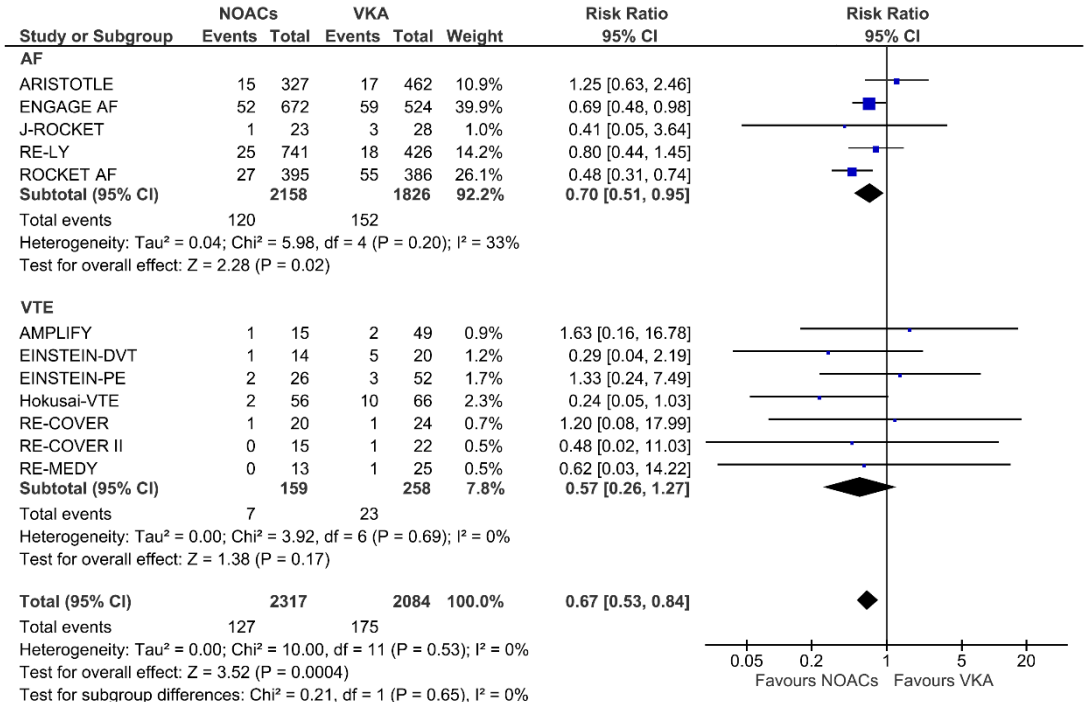

Figure 17: Forest plot of major bleeding case-fatality risk associated with NOACs.

Post-major bleeding all-cause mortality risk analysis

Only AF studies presented data for all-cause mortality following major bleeding events. RE-LY (dabigatran vs. VKA)[70] and ARISTOTLE (apixaban vs. VKA)[109] provided 30-days post major bleeding mortality, while ROCKET AF (rivaroxaban vs. VKA)[110] data were not limited to the 30-days post-index event. Except for ROCKET AF, data were adjusted for multiple variables.

Pooled analysis of these trials was taken using odds ratio in order to preserve the original estimates obtained after adjustment to potential confounders. NOACs showed a significant 43% odds reduction in the risk of all-cause mortality in major bleeding survivors (OR 0.57, 95%CI: 0.45 to 0.73; I^2=0%) (Figure 18). Adjusting the data to the 30-days mortality rate reported by Majeed and colleagues[121], 78 deaths (95%CI: 63 to 98) would have been avoid per 1000 patients surviving to a major bleeding event treated with NOACs compared to VKA.

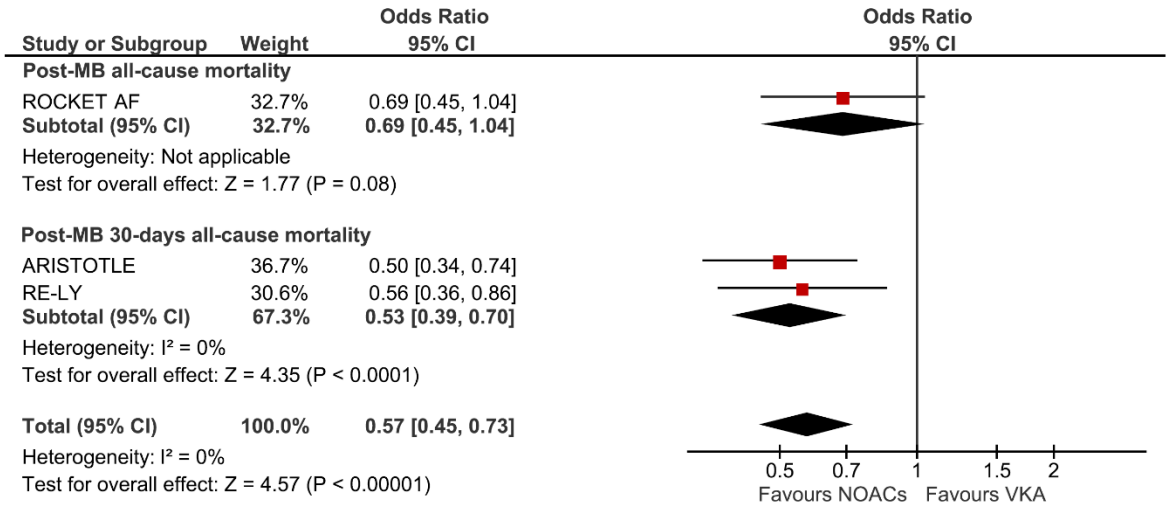

Figure 18: Forest plot of meta-analysis evaluating the mortality after a major bleeding events with NOACs and VKA.

Outcome results according to NOAC

NOACs were comparable in terms risk of major bleeding risk and fatal events associated with major bleeding, either for AF, VTE or overall. The risk reductions for all the above presented outcomes among the different NOACs are depicted in Figure 19.

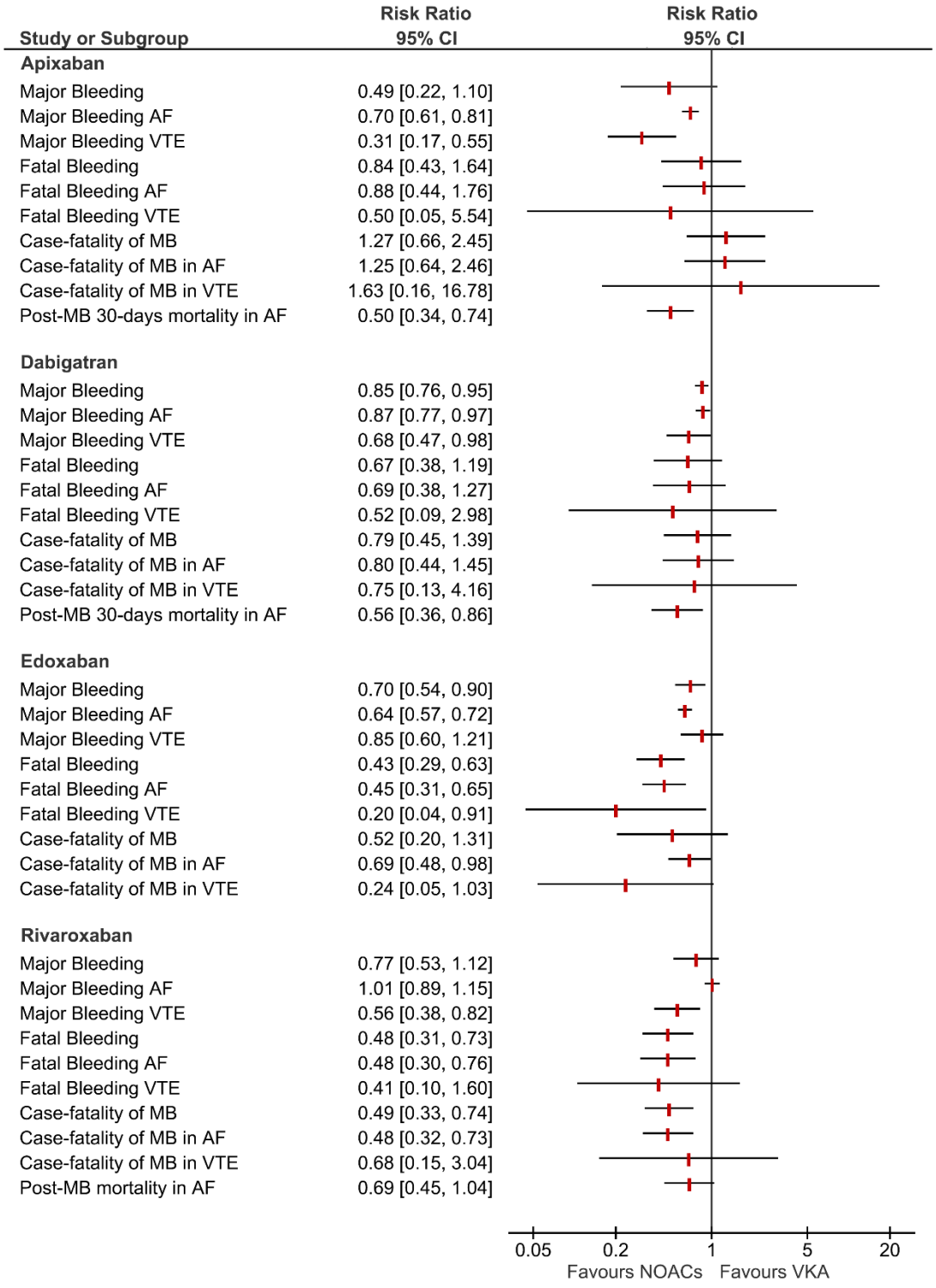

Figure 19: Risks of major and fatal bleeding associated to each individual NOAC.

CONCLUSIONS

Pooled analysis from randomized controlled data shows that NOACs significantly decreased the risk of fatal bleeding in patients with AF and VTE compared to VKA (with or without an initial stage with LMWH). In patients with AF these drugs were also associated with a significant decreased risk of all-cause mortality in major bleeding survivors. Major bleeding case-fatality was also significantly reduced in this context. Despite the absence of specific antidotes, NOACs did not show an increased risk of mortality associated to the bleeding event. Inversely, these drugs were likely to improve these outcomes.

3.2.2. Major gastrointestinal bleeding

BACKGROUND

Gastrointestinal (GI) bleeding is the most frequent cause of major bleeding accounting for 30-40% of the overall major bleeding events [121-124] and some studies have shown an increased risk of GI bleeding among NOAC treated patients [70,110]. A previously published systematic review have also associated NOACs with an increased GI major and clinically-relevant non-major bleeding risk [125]. However, the overall severity of this 'class effect' is not known and requires a comprehensive evaluation of major GI bleeding events, rather than clinically relevant bleedings. Therefore, the risk of major GI bleeding associated to NOACs was evaluated, through a systematic review with meta-analysis of randomized controlled trials (RCTs).

METHODS

This was a systematic review and meta-analysis of randomized controlled trials (full methodology detailed the published version of the article and briefly explained in the Section 3.1) reporting data for GI bleeding events comparing NOACs, against VKA (with or without an initial stage with concomitant LMWH in patients with atrial fibrillation (AF) or venous thromboembolism (VTE).

Primary outcome was major GI bleeding, as defined by the International Society on Thrombosis and Hemostasis (ISTH) [95].

RESULTS

Twelve studies with 102790 patients were analysed[70,109-120]: 5 RCTs with AF patients,[70,109-112] and 7 studies with VTE patients.[113-120].

Mean follow-up period ranged from 1 to 2.8 years for AF trials, and most of VTE patients had a 6 months of follow-up.

Major GI bleeding risk analysis

Five RCTs evaluated 72961 patients with AF, comparing NOACs with VKA.[70,109-112] Compared to VKA, NOACs were not associated with an increased risk of major GI bleeding (RR 1.08; 95%CI: 0.85 to 1.37, I^2=78 %, Figure 20)

Seven RCTs evaluated a total of 29829 patients with VTE and compared NOACs with VKA (with or without initial treatment with LMWH) [113-120]. Major GI bleeding risk was not different between NOACs and VKA (RR 0.77, 95%CI: 0.49 to 1.21, I^2=43 %, Figure 20).

Overall, NOACs were comparable to VKA (± LMWH) in 12 RCTs enrolling 102790 patients with AF or VTE, as no differences were found in the pooled major bleeding risk (RR 0.97, 95%CI: 0.78 to 1.29; I^2=66%; Figure 20).

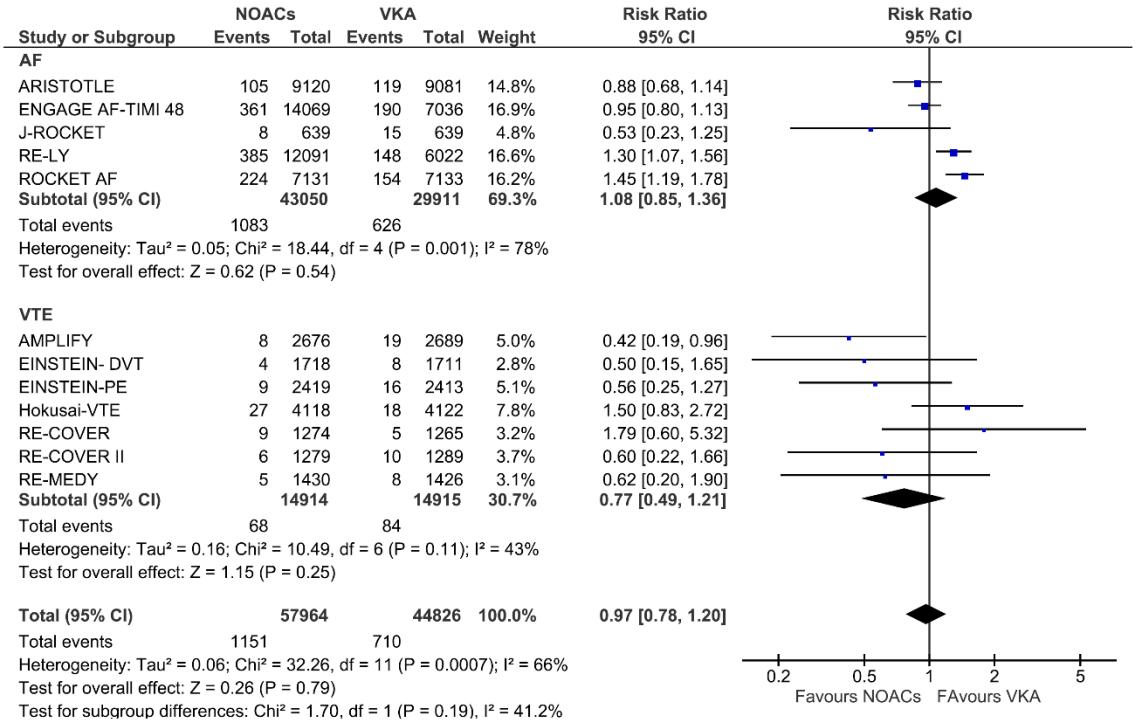

Figure 20: Forest plot of major GI bleeding risk associated to NOACs compared with VKA.

Figure 20 shows the results of the pooled analysis of major GI bleeding risk of NOACs compared to VKA, and Figure 21 shows the risk of major GI bleeding with each individual NOAC. None of the NOACs individually were associated with an increased risk of major GI bleeding, and there were no significant differences among them.

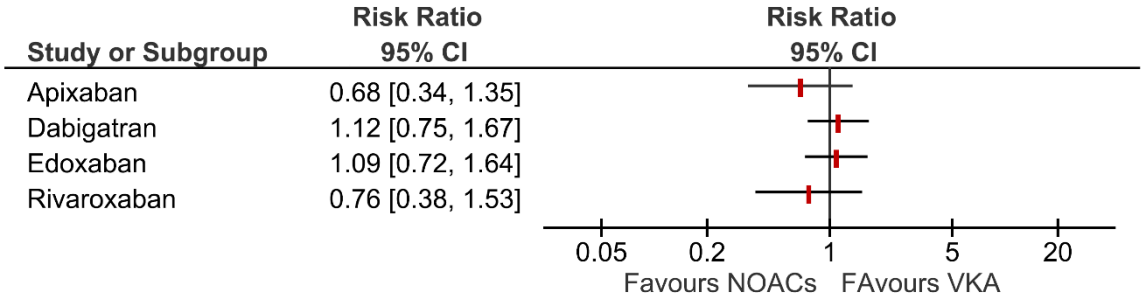

Figure 21: Pooled major GI bleeding risks of each NOAC compared with VKA.

CONCLUSIONS

The main conclusion of this systematic review is that NOACs, overall, did not increase the risk of major GI bleeding. Even with the established proneness to GI bleeding associated to NOACs, these data suggest that it is not due to severe events.[125]

3.2.3. Intracranial hemorrhage

BACKGROUND

Anticoagulants pose an increased risk of bleeding [126]. Amongst the many possible different bleeding events, both in terms of location and severity, intracranial hemorrhage (ICH) is by far the most feared due to the increased morbidity and lethality [127,128]. In RCTs, NOACs risk of major bleeding events has been heterogeneous [129,130], and uncertainty exists regarding a putative "protective" effect of NOACs in comparison to other antithrombotic drugs through all indications, as well as the clinical relevance of this effect. Therefore, NOACs ICH risk was analysed through a systematic review of RCTs.

METHODS

This was a systematic review and meta-analysis of randomized controlled trials (full methodology detailed the published version of the article and briefly explained in the Section 3.1) reporting data for ICH comparing NOACs, against VKA or sequential treatment of LMWH and VKA in patients with atrial fibrillation (AF) or venous thromboembolism (VTE). The outcome of interest was intracranial hemorrhage (ICH), a component of major bleeding according to the International Society of Thrombosis and Haemostasis.[95]

RESULTS

Overall 11 RCTs (99346 patients) reporting data about ICH, and comparing NOACs with VKA, were included: 5 trials evaluating AF (72961 patients) patients[70,109-112], and 6 trials with VTE patients (26385 patients)[113-119].

Intracranial hemorrhage risk analysis

Pooled analysis of AF trials showed a significant 56% ICH risk reduction (RR 0.44, 95%CI: 0.35 to 0.55), with moderate statistical heterogeneity (I^2=49%) (Figure 22). NNT to avoid 1 ICH was 123 (95%CI: 105.8 to 152.8), and the ICH events saved *per* 1000 patients treated with NOACs were 8 (95%CI: 6.5 to 9.5).

In VTE patients the comparison of NOACs with VKA (with or without the sequential treatment with LMWH), showed with a significant 69% risk reduction of ICH risk with NOACs (RR 0.37, 95%CI: 0.18 to 0.74), without statistical heterogeneity (I^2=0%) (Figure 22).

NNT to prevent one ICH compared to VKA was 714 patients (95%CI: 615.2 to 888.6) during an average of 7 months. This means that 1 ICH event (95%CI: 1.1 to 1.6) is avoided *per* 1000 patients treated with NOACs compared to VKA.

Globally NOACs significantly reduced the risk of ICH by 57% (RR 0.43, 95%CI: 0.36 to 0.51) compared to VKA. In terms of absolute risk assessment, NOACs owe a NNT of 162 patients (95%CI: 143.9 to 188.0) and 6 patients without ICH (95%CI: 5.3 to 6.9) *per* 1000 treated with NOACs.

The forest plot with the pooled analysis of ICH risk associated with NOACs is illustrated in Figure 22. Figure 23 shows that the ICH risk reduction is transversal to all NOACs.

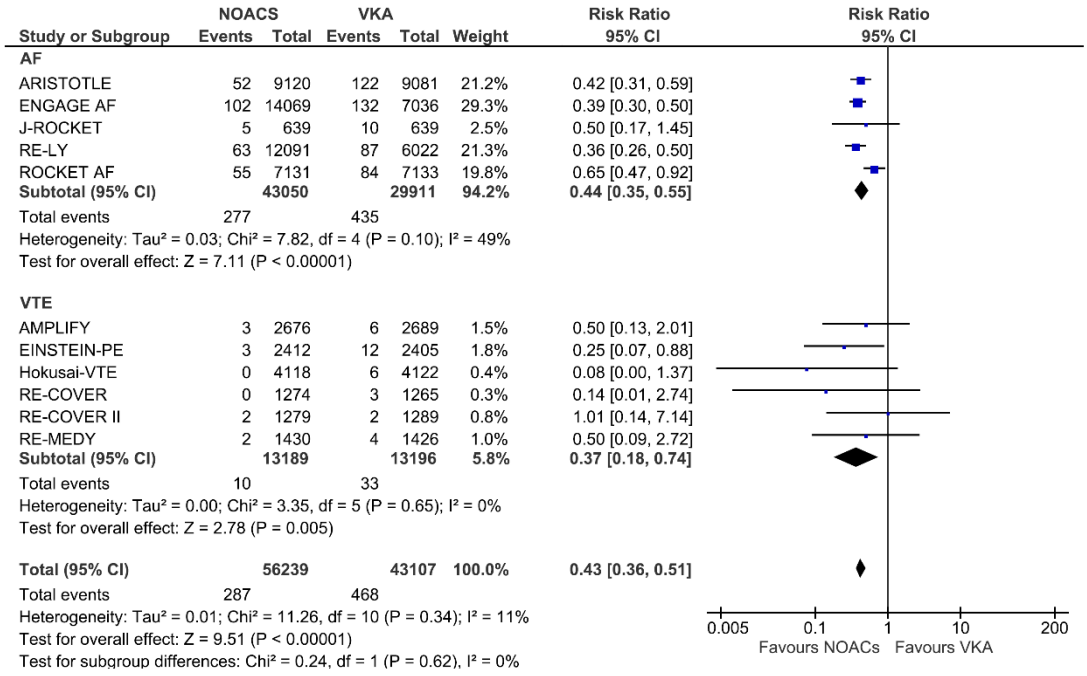

Figure 22: Forest plot with risk of intracranial hemorrhage with NOACs in comparison to VKA.

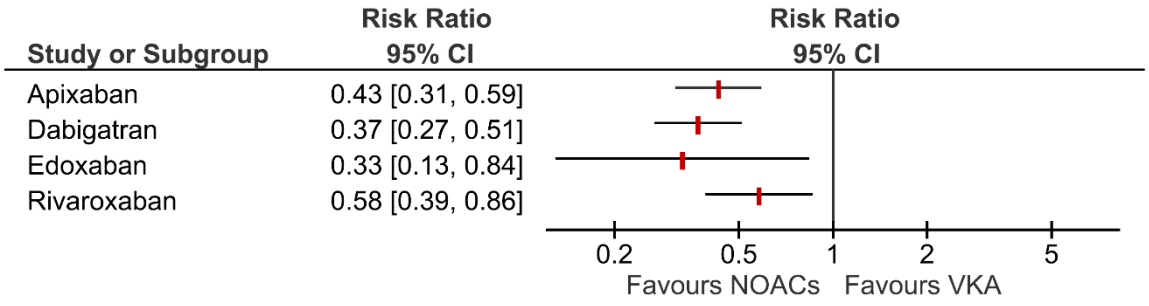

Figure 23: Pooled ICH risks of each NOAC compared with VKA.

CONCLUSIONS

Intracranial hemorrhage is a well-known and lethal complication of anticoagulant drugs [131,132]. Knowing that this the bleeding site most commonly associated to disability and mortality, the results here obtained are of paramount importance. It is not well established the reason for NOACs superiority, however it is known that cerebral vessels hemostasis is likely to be highly dependent on the tissue factor/factor VIIa interaction to primarily initiate the coagulation process. Unlike VKA, which block the carboxylation process and inhibit the production of functional factor VII, among other coagulation factors, NOACs directly and selectively inhibit factor IIa or Xa without interfering with the primary hemostatic mechanism of cerebral vessels.

In conclusion, for patients requiring anticoagulation treatment, the risk of ICH is about half with NOACs in comparison to VKA (with or without LMWH).

3.2.4. Other major bleeding sites: intraocular and pericardial hemorrhages.

BACKGROUND

Intraocular and pericardial hemorrhages are quite important due to their potential consequences.

Although rare [19], substantial intraocular hemorrhages can cause severe visual acuity impairment and, in some cases, surgery is needed for complete resolution [133].

Pericardial hemorrhages with NOACs have been seldom reported, but their consequences can be lethal [134].

Therefore, to better estimate the risk of these clinically-relevant bleedings (event defined by default as a major bleed according to the ISTH definition[95]) with NOACs, a systematic review and meta-analysis of RCTs was performed.

METHODS

This was a systematic review and meta-analysis of randomized controlled trials (full methodology detailed the published version of the article and briefly explained in the Section 3.1) reporting data for intraocular or pericardial hemorrhages comparing NOACs, against VKA.

RESULTS

Ten RCTs (91106 patients) were included with data for intraocular bleeding [70,109-119], and 6 trials (79083 patients) reported pericardial bleeding[70,109,110,112,115,119].

Intraocular hemorrhage risk analysis

No difference was identified between NOACs and VKA among both AF (RR 0.84, 95%CI: 0.59 to 1.19, I^2=35%) and VTE patients (RR 0.67, 95%CI: 0.37 to 1.20, I^2=0%) (Figure 24).

The overall analysis confirmed the absence of evidence for increased risk of substantial intraocular bleeding was associated with NOACs (RR 0.79, 95%CI: 0.61 to 1.03; I^2=8%) (Figure 24).

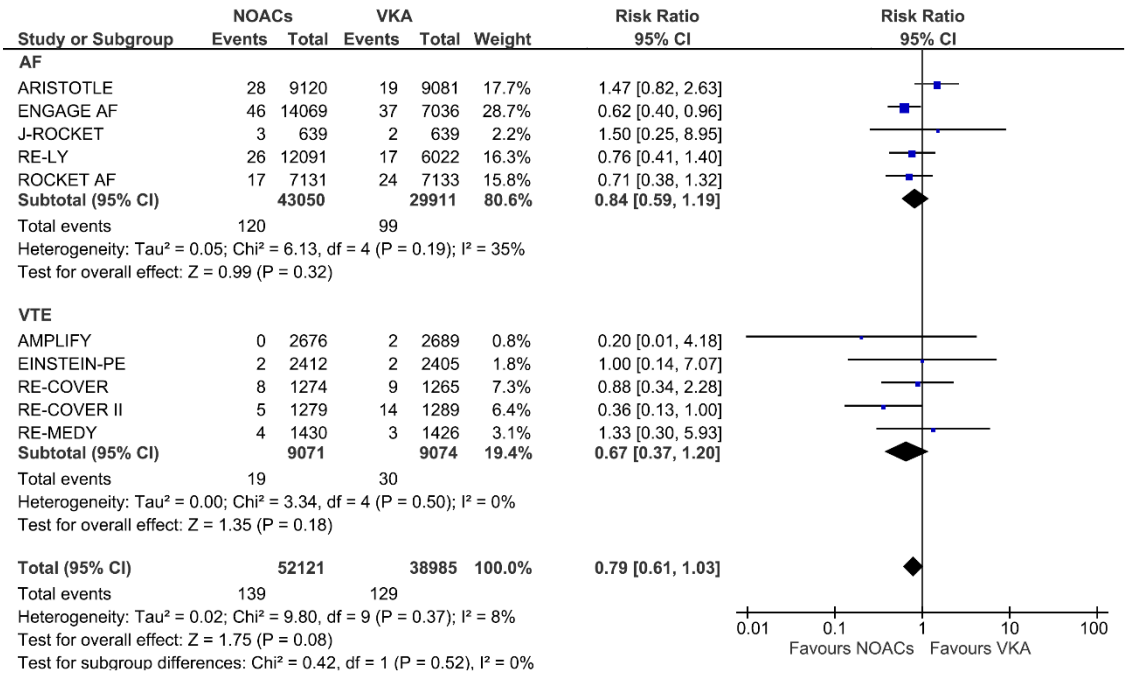

Figure 24: Forest plot with results of pooled analysis regarding intraocular bleeding.

Pericardial bleeding risk analysis

Pooled results also did not show an increased risk of pericardial bleeding with NOACs in AF setting (RR 1.06, 95%CI: 0.37 to 3.06), VTE patients (RR 0.26, 95%CI: 0.03 to 2.31), or in the overall analysis (RR 0.81; 95%CI: 0.31 to 2.11) (Figure 25). No heterogeneity was noticed across studies estimates (I^2=0%).

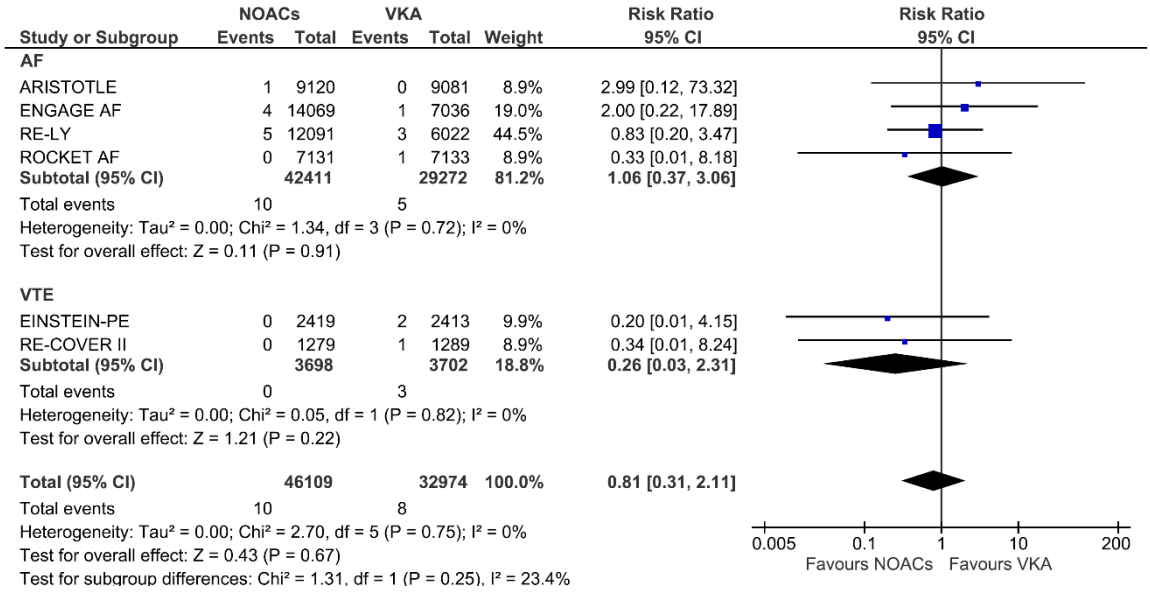

Figure 25: Forest plot with the results of the pooled analysis regarding pericardial bleeding.

As expected, due to the rare frequency of these events, individual NOACs were not associated to an increased or decreased risk of intraocular or pericardial bleeding.

The Figure 26 shows the estimated for each individual NOAC.

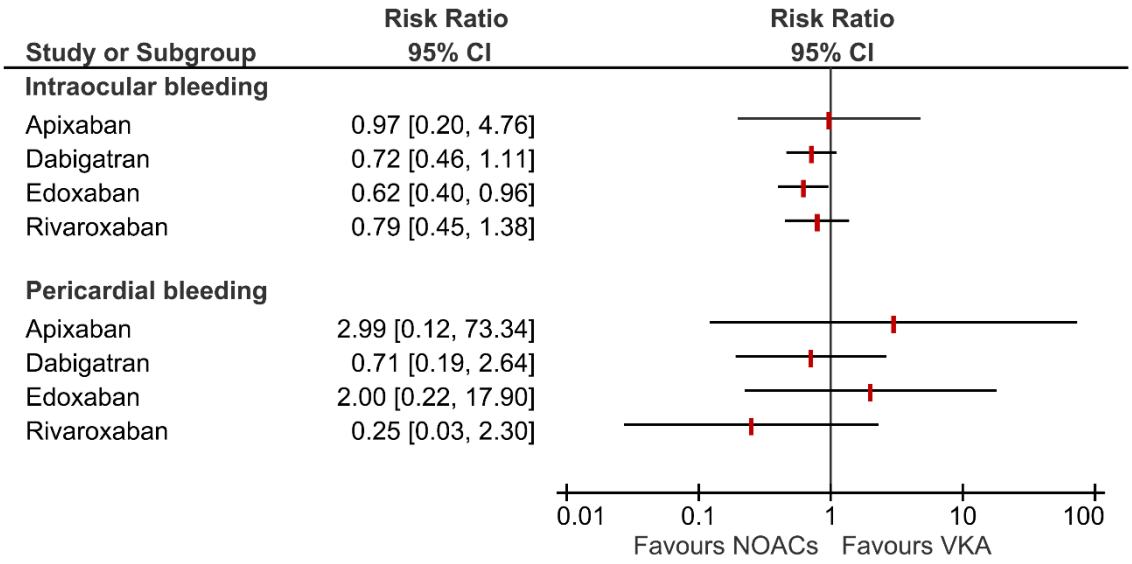

Figure 26: Estimates of pooled analysis for each individual NOAC regarding intraocular and pericardial bleeding.

CONCLUSIONS

These results highlight the absence of evidence about differences in the risk of intraocular and pericardial hemorrhages between NOACs and VKA (with or without LMWH).

For intraocular hemorrhage, only substantial events such as hyphema, vitreous hemorrhage, subretinal hemorrhage and suprachoroidal hemorrhage were considered as major bleeding events. This definition respects the criteria established by ISTH [95], excluding minor uncomplicated bleedings, such as subconjunctival hemorrhages.

Pericardial hemorrhages are very rare, but potentially, life-threatening clinically events. Based on the best available evidence, no safety alert can be raised for an increased risk of pericardial or intraocular bleeding with NOACs.

3.3. Non-bleeding adverse events

While most of the safety issues regarding antithrombotic drugs mainly rely on the clinical assessment of the pharmacodynamics consequences, such as bleeding (reported the previous section), other pharmacokinetics-related adverse events or other possible off-target effects can arise and must be scrutinized in order ensure the safety of drugs.

Liver and kidneys are the main organs for overall drug metabolism and excretion.

All oral anticoagulants, with exception of dabigatran, are metabolized by liver cytochrome P450. Furthermore, the recent history of ximelagatran (an oral direct thrombin inhibitor) post-marketing withdrawal due increased risk of liver injury[51], increases the need of safety reassurance regarding the hepatic safety of NOACs.

All oral anticoagulant drugs (NOACs and VKA) are at least in some extent excreted in the urine. Acute kidney injury episodes related to anticoagulant treatment was recently described and deemed to have a prognostic impact[135].

For the reasons previously mentioned, drug-induced liver injury and renal dysfunction risks of NOACs were assessed in this section.

Other outcomes evaluated in this section, such as insomnia and infections, were elicited by the unexpected findings in trials or observational studies, and anecdotal case report letters.

As none of the mentioned outcomes are expected to be related to specific conditions or other known anticoagulant drugs, to further increase the power of the analysis, other conditions and comparator (other than AF and VTE; and VKA, respectively), were considered for the analysis of the risk of non-bleeding adverse events.

3.3.1. Drug-induced liver injury

BACKGROUND

Drugs are frequently metabolized in the liver [136]. Drug-induced liver injury (DILI) includes a broad clinical and pathologic spectrum of hepatotoxicity, and many genetic and non-genetic patient characteristics have been proposed as risk factors for DILI from medications [137,138]. In recent years, safety alerts have been made warning for the risk of DILI, including life-threatening liver failure, caused by cardiovascular drugs. For example, dronedarone, an antiarrhythmic drug, can cause serious liver injury [139], and ximelagatran, an oral direct thrombin (IIa) inhibitor, has been withdrawn from the market in 2004 due to the risk of DILI [51]. These safety warnings only emerged with post-marketing experience because hepatic adverse drug reactions due to cardiovascular drugs are relatively uncommon, but potentially serious, and premarketing clinical trials are underpowered to detect differences between treatment arms. These recent high profile cases of serious liver adverse reactions associated with cardiovascular drugs have amplified the need for careful pre-marketing analysis of DILI risk associated safety.

Therefore, a systematic review and meta-analysis of randomized controlled trials was performed to better estimate the risk of hepatic adverse drug reactions associated with NOACs.

METHODS

This was a systematic review and meta-analysis of randomized controlled trials (full methodology detailed the published version of the article and briefly explained in the Section 3.1). All RCTs were considered for inclusion irrespective of patients' disease, comorbidities, background therapy, NOAC treatment duration or follow-up. Only trials reporting hepatic data as a pre-specified outcome were included to avoid selective reporting. Trials had to provide laboratory data for transaminases and bilirubin.

Primary outcome was DILI, defined as increases in serum levels of transaminases above three times the upper limit of normal (ULN) and total bilirubin above two times the ULN. According to Hy's law, the outcome defined above is the most specific predictor of potential severe hepatotoxicity [96]. Secondary outcomes were incidence of transaminases elevation >3x ULN, and incidence of bilirubin elevation >2x ULN.

RESULTS

For DILI analysis, 26 studies enrolling 161800 patients were included[39,70,109-115,117-120,140-151]. About 90912 of these patients were treated with NOACs. The NOACs evaluated were apixaban (7 RCTs; 45122 patients) [39,109,140-144], dabigatran (7 RCTs; 31670 patients) [70,113,118,119,145,146], edoxaban (2 RCTs; 28848 patients)[112,117], and rivaroxaban (10 RCTs; 56160 patients)[110,111,114,115,120,147-151].

Patients' mean age varied between 55 and 71 year-olds across trials. About 30% (43 130 patients) of the patients had AF. The weighted mean follow-up was 16.6 months (range, 2 weeks to 2.8 years).

Low-molecular weight heparin (LMWH) was the most common control group as it was included in 39% of the studies.

For transaminases elevation analysis, 25 trials with 145164 patients were included[39,70,109,111,113,114,116,118,120,140-142,144-147,149-154]: 7 RCTs with apixaban (47838 patients) [39,109,116,140-142,144], 8 RCTs with dabigatran (31670 patients) [70,113,118,145,146,152,153], 2 RCTs with edoxaban (28848 patients) [112,117], and 8 RCTs with rivaroxaban (33519 patients)[111,114,120,147,149-151,154].

Bilirubin elevation was studied in 9 RCTs including 41692 patients[70,116,118,140-142,147,150,151]. These trials evaluated the following NOACs: apixaban (4 RCTs; 16723 patients)[116,140-142], dabigatran (2 RCTs; 19476 patients)[70,118], and rivaroxaban (3 RCTs; 5493 patients)[147,150,151].

Risk of DILI (transaminases >3x ULN with total bilirubin >2x ULN) analysis

Pooled analysis of 26 studies showed that NOACs does not increase the risk of DILI (transaminases >3x ULN with total bilirubin >2x ULN). The RR was 0.93 (95%CI: 0.75 to 1.15). Individually, none of the NOACs increased the risk of DILI and no differences were found between NOACs (p=0.31) in the risk of DILI against control. There was no heterogeneity among studies results (I^2=0%). Figure 27 shows the detailed results for this outcome

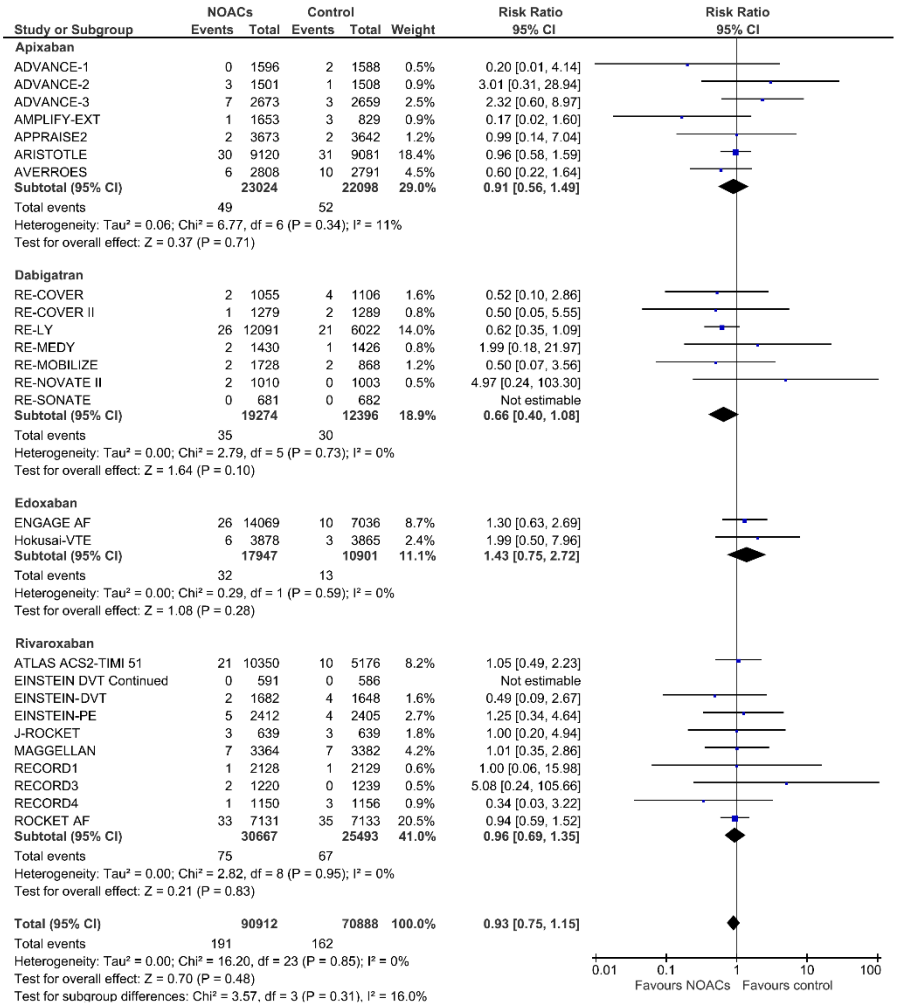

Figure 27: Forest plot with results of DILI (elevation of transaminases >3x ULN and of total bilirubin>2x ULN) risk pooled analysis. ULN: upper limit of normal.

Risk of transaminases elevation (3x ULN) analysis

Interestingly, NOACs were less likely than controls to have transaminase elevations >3x ULN (RR 0.81; 95%CI: 0.72 to 0.91) (Figure 28). Moderate heterogeneity (I^2=47%) was found between studies. This "protective" effect was apparently higher among LWMH-controlled studies. Therefore, an exploratory analysis according to the control group of the trials was performed.

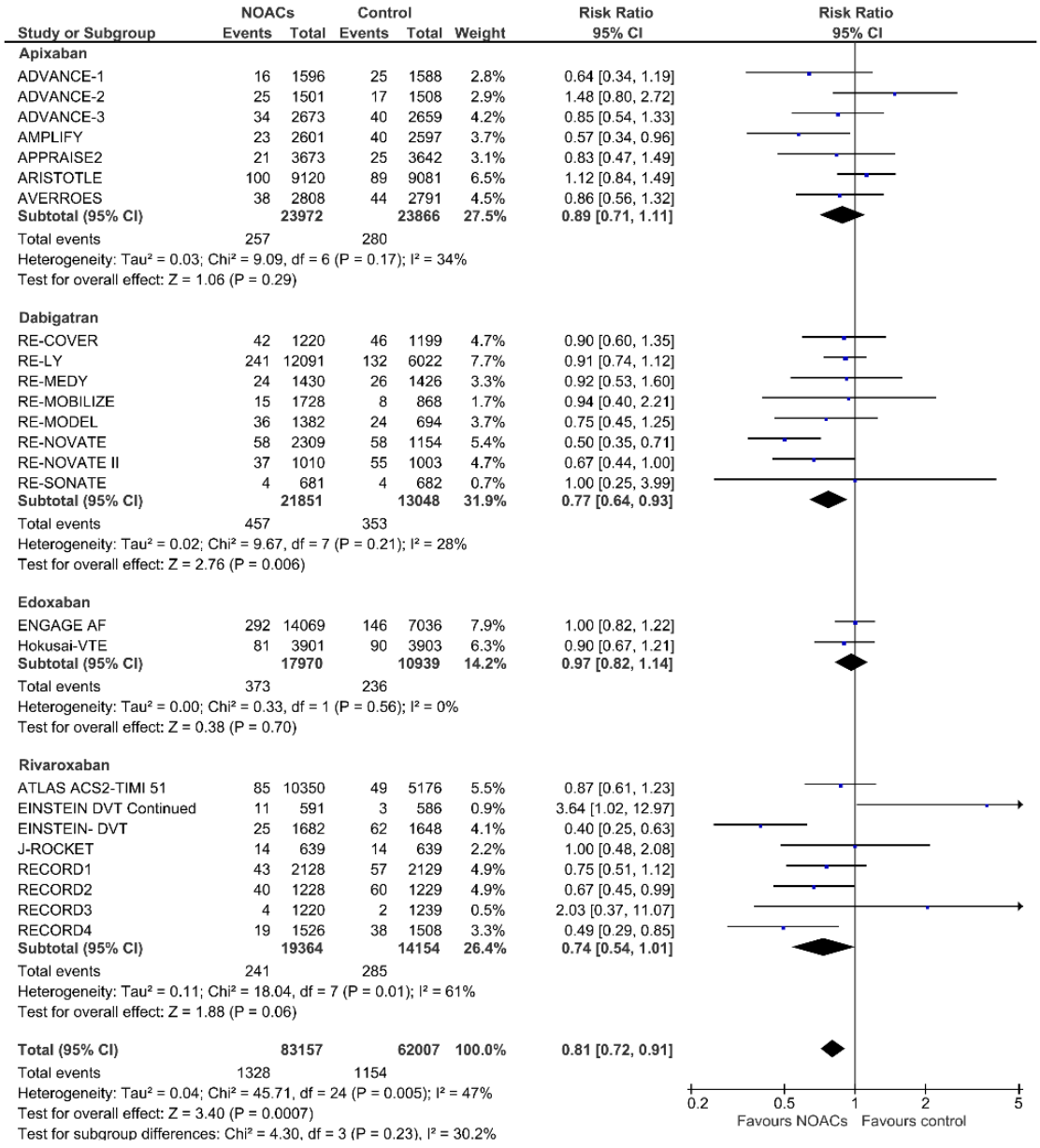

Figure 28: Forest plot of transaminases elevation (3x ULN) risk associated to NOACs.

Pooled results from LMWH-controlled trials showed a 29% risk reduction (RR 0.71; 95%CI: 0.59 to 0.85; data not shown in figures) of transaminases elevations among NOAC treated patients in comparison to LWMH, with low-to-moderate heterogeneity (I^2=27%). Pooled results from other trials showed non-significant reductions in the risk of transaminases elevation.

Risk of bilirubin elevation (2x ULN) analysis

In terms of bilirubin elevation, NOACs were similar to controls with a RR 0.98 (95%CI: 0.61 to 1.56; I^2=45%) (Figure 29).

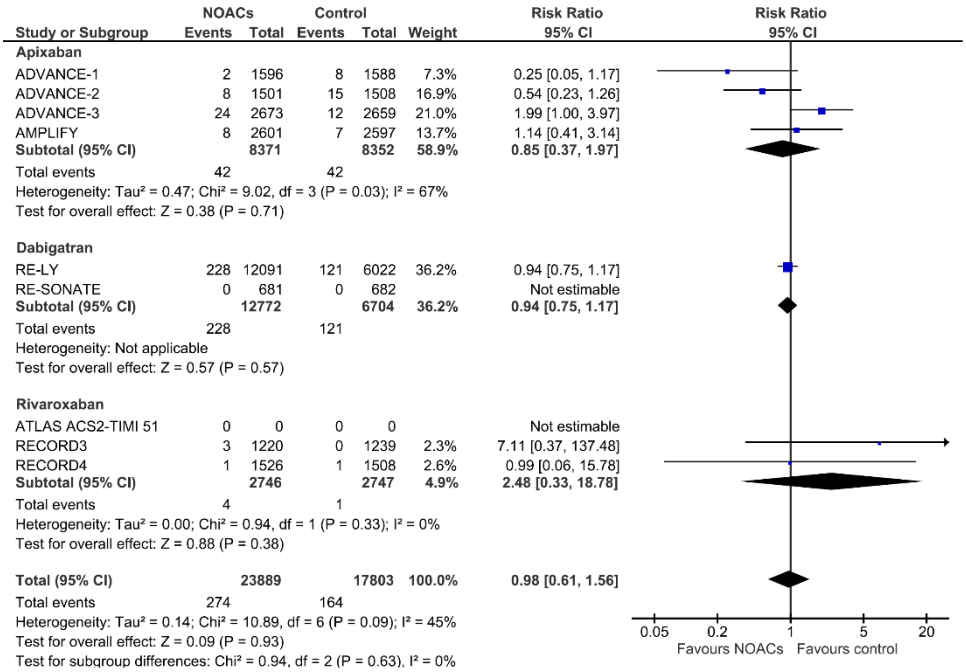

Figure 29: Forest plot of bilirubin elevation (2x ULN) risk associated to NOACs.

CONCLUSIONS

The main findings of this systematic review are that NOAC are not associated with an increased risk of DILI, based on pooled estimates from large RCTs. Globally, DILI is an uncommon event from a population perspective with an annual incidence rate of 1-2 events *per* 1000 patients[155]. Due to the potential severity of this adverse event it is important to estimate the risk of DILI in the most possible precise way and as soon as possible during the early phase of drug development and before massive post-marketing use. Meta-analysis increases the power to detect group differences. In the case of NOAC, the present meta-analysis included data from more than 150 000 patients, more than half exposed to NOAC treatment during a mean duration of 16 months.

3.3.2. Renal dysfunction

BACKGROUND

All NOACs (with different extensions) are somehow excreted by the kidneys, meaning that in patients with severe renal dysfunction the concentration of anticoagulant and its effects increase. Safety in this setting is not assured as pivotal clinical studies did not include patients with estimated glomerular filtration rate <25 mL/min.

Furthermore, the recent description of acute kidney injury episodes associated to anticoagulant treatment deserved the attention of the scientific community[135]. Therefore, to adequately evaluate NOACs in terms of renal failure, which by itself may impose important changes in the pharmacokinetics (or in the indication of use), a systematic review and meta-analysis of RCTs was performed.

METHODS

This was a systematic review and meta-analysis of randomized controlled trials (full methodology detailed the published version of the article and briefly explained in the Section 3.1). All RCTs were considered for inclusion irrespective of patients' disease, comorbidities, background therapy, NOAC treatment duration or follow-up. Trials had to provide data about renal dysfunction or laboratory markers of kidney function.

Primary outcome was renal failure reported by investigators as an adverse event (or serious adverse event) or an increase of creatinine or blood urea nitrogen deemed to be significant by investigators.

RESULTS

Eleven trials reported the outcome of interest[70,109-112,118,119]. These trials enrolled overall 90768 patients. Seven of these were VKA-controlled trials (with or without an initial stage with concomitant LMWH): 5 AF RCTs[70,109-112] and 2 VTE RCTs[118,119], with overall 78385 patients. The remaining were rivaroxaban LMWH-controlled trials with patients that underwent orthopedic surgery[149-151,154]. The mean age of patients included in RCT ranged from 55 to 73 years. Follow-up varied between 1 month (post-orthopedic surgery thromboprophylaxis RCTs) and 2.0 years. No trial included patients with estimated glomerular filtration rate <25 mL/min.

Renal failure as increase of serum creatinine was the outcome sought in three studies[109,118,119], treatment-emergent adverse event (TE AE) for one study[111], and treatment-emergent serious adverse events (TE SAE) for 3 studies[70,110,112].

For RECORD (1-4) studies[149-151,154], a series of trials evaluating rivaroxaban versus low-molecular weight heparin (LMWH) in patients undergoing orthopedic surgery, 2 outcomes of interest were available: overall TE SAE acute renal failure for all the 4 trial together; and high/increase of serum creatinine, separately for RECORD1-2[149,154], and RECORD3-4[150,151].

Renal failure risk analysis

Data from 10 RCTs with 75100 patients were included for analysis (40507 treated with NOACs).

Primary analysis of renal failure as a treatment-emergent serious adverse event (TE SAE) did not associate NOACs to this outcome (RR 0.93; 95%CI: 0.82 to 1.05; I^2=0%), among 65837 patients (Figure 30).

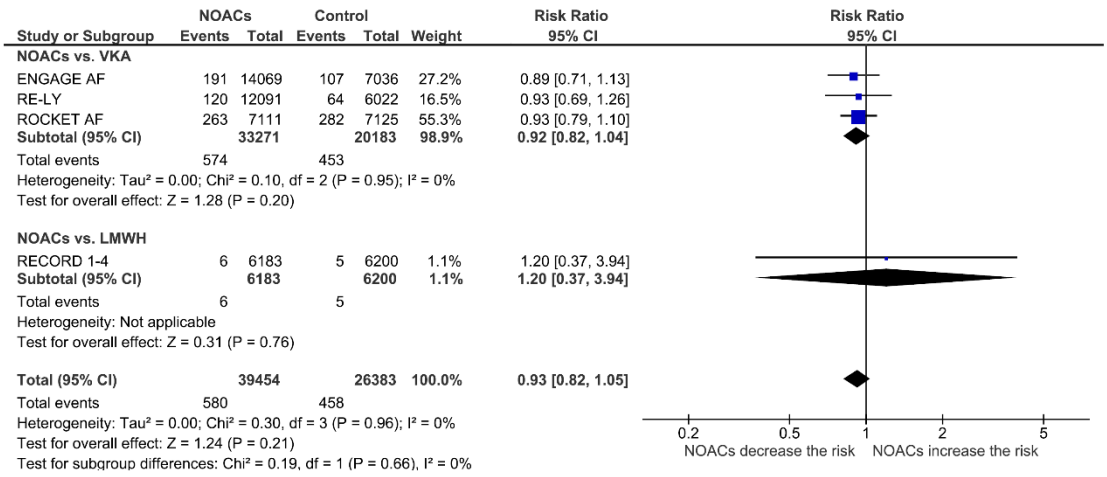

Figure 30: Forest plot with evaluation of NOACs risk of renal failure as treatment-emergent SAE.

The use of other outcomes was remarkable in RECORD1-2 (increase of serum creatinine) for an increase of renal failure risk in rivaroxaban arm compared to LMWH (RR 1.29, 95%CI: 1.11 to 1.50). Nevertheless, the analysis of the primary outcome (TE SAE renal failure), ensures safety and does not confirm this proneness in terms of severity in a larger population.

Analysis according to renal failure definition was performed (Figure 31).

J-ROCKET that was the only study reporting TE AE renal impairment and significant increased risk of this adverse event was noticed in this trial (Figure 31). The pooled results of other renal failure definitions did not show an increased risk of renal failure with NOACs (Figure 31).

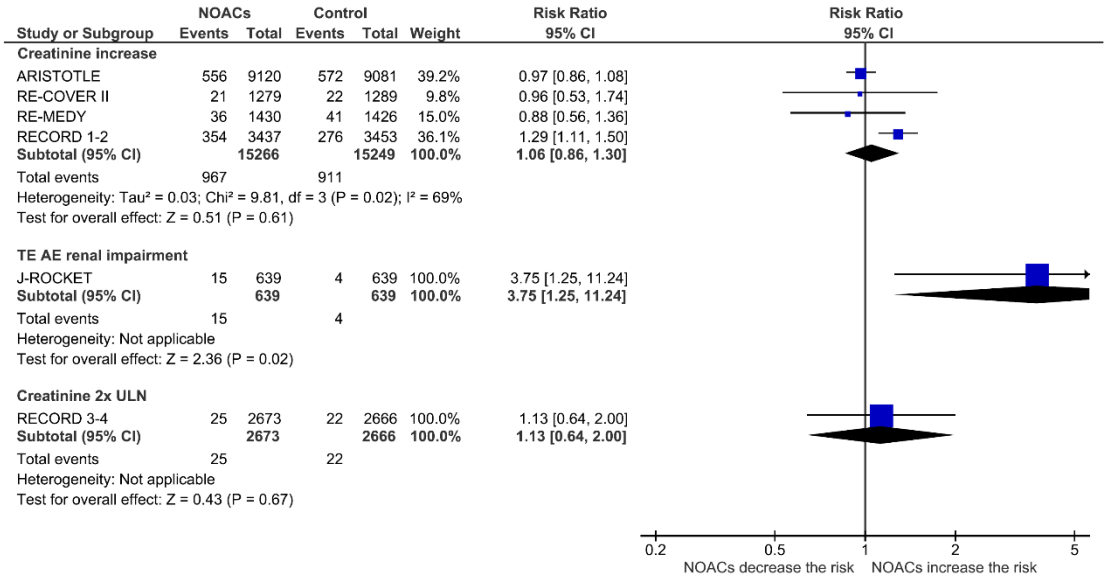

Figure 31: Risk of renal dysfunction with NOACs according to the outcome definition. AE: Adverse event; ARF: Acute renal failure; TE: Treatment-emergent; ULN: Upper limit of normal.

CONCLUSIONS

NOACs did not show an increased risk of serious renal failure compared to other anticoagulants drugs. Rivaroxaban showed an increased risk of creatinine elevation in trials of thromboprophylaxis after hip or knee surgery. Surveillance should be warranted in order to confirm or refute these data.

3.3.3. Insomnia

BACKGROUND

Insomnia is common sleep disorder characterized by difficulty to initiate or maintain sleep[156]. This condition can lead to impaired life quality and inability to adequately perform many tasks of daily living activities[157,158].

Darexaban, is an anti-Xa oral anticoagulant discontinued in the clinical development stage due to the lack of partnerships for large clinical development and commercialization[159]. In a phase III randomized mechanical prophylaxis-controlled trial, darexaban showed high rates of insomnia, although it was not different than the proportion of insomnia reported in patients with mechanical thromboprophylaxis[160]. Insomnia is known to be an important adverse event associated to mechanical thromboprophylaxis[161], and similar rates of insomnia obtained between darexaban and thromboprophylaxis were not expected. However, since the trial had an open-label design, the perception of adverse events by patients and/or physicians may have been biased[162]. Furthermore, insomnia related adverse events may be reported in a subjective manner[163].

These reasons support the aim of the systematic review of RCTs, in order to reassure the safety profile of approved NOACs, which are related to darexaban, in terms of insomnia.

METHODS

This was a systematic review and meta-analysis of randomized controlled trials (full methodology detailed the published version of the article and briefly explained in the Section 3.1). All RCTs were considered for inclusion irrespective of patients' disease, comorbidities, background therapy, NOAC treatment duration or follow-up. Trials had to provide data about the adverse event insomnia as reported by investigators.

Beyond the considered NOACs (apixaban, dabigatran, edoxaban, rivaroxaban), darexaban's trial (Sakon et al[160]; despite of the discontinuation in the development) was included because the results of this trial motivated this analysis.

RESULTS

Seven phase RCTs reported the frequency of insomnia as an adverse event[140,144,146,149,150,153,160]. Overall these trials included 23023 patients.

Insomnia risk analysis

Overall, the meta-analysis showed that NOACs did not increase the risk of insomnia, RR 0.94 (95%CI 0.83-1.08; I^2=0%), and no differences were found between each of these drugs (p=0.97). Figure 32 shows the forest plot of the meta-analysis.

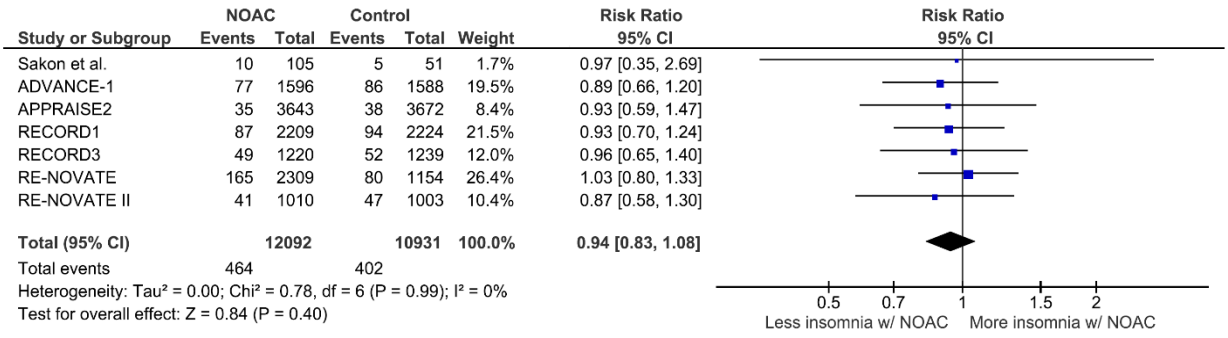

Figure 32: Pooled risk of insomnia with NOACs, including darexaban.

One of the purposes of this review was to evaluate whether the study design (open label vs. blinded studies) had an impact in the risk of insomnia. In blinded studies, NOACs were not associated to increased risk of insomnia (RR 0.94, 95%CI 0.83-1.08; I^2=0%).

CONCLUSIONS

This systematic review did not show increased risk of insomnia with NOACs. This question was driven by the results of a RCT comparing darexaban with mechanical prophylaxis in the prevention of venous thromboembolism in patients undergoing major abdominal surgery[160]. One of the points of interest of this trial was its open-label design, with the reported incidence of insomnia being high despite the absence of differences among the interventions. The risk of insomnia with mechanical thromboprophylaxis was expected to be higher compared to darexaban, and study design was hypothesized explain differences in the estimates. The results of this meta-analysis showed that NOACs were also not associated to insomnia in blinded studies, regardless of the comparators.

3.3.4. Infections

BACKGROUND

There is a bilateral relationship between inflammation and coagulation[164,165]. Inflammation is an important component of the innate immune system. Acute inflammation as arises in systemic infections (sepsis) is known to activate the coagulation system being possible to occur disseminated intravascular coagulation, a potentially lethal complication of sepsis. It is generally accepted that there are 3 mechanisms for this prothrombotic complication: cytokine-induced tissue factor expression; the downregulation of activated protein C (a endogenous anticoagulant; see Chapter I); and decreased fibrinolysis[164]. Inversely, coagulation may prompt to or enhance the immune response. Coagulation factors such as thrombin and factor Xa can activate protease-activated receptors (PARs), increase the endothelial adhesion and chemotaxis of leucocytes, and the production of cytokines[166].

Considering the role of thrombin and factor Xa in the immune response, some doubts were raised concerning the role of the NOACs in the proneness to infections[167]. In fact some have elicited this link based on observational studies (higher rate of wound complications after orthopedic surgeries[168], and anecdotal case reports connecting NOACs to infections (particularly urinary tract infections)[169].

To further clarify this link, a systematic review and meta-analysis of RCTs with data about overall infections, post-surgery infections and urinary tract infections was performed.

METHODS

This was a systematic review and meta-analysis of randomized controlled trials (full methodology detailed the published version of the article and briefly explained in the Section 3.1). All RCTs were considered for inclusion irrespective of patients' disease, comorbidities, background therapy, NOAC treatment duration or follow-up. Trials had to report data about all infections, urinary infections and post-surgery infections.

RESULTS

Twelve RCTs reporting outcomes of interest were included[39,70,109,110,112,115,144,146,149-151,154].

Infection risk analysis

Pooled analysis of 8 RCTs (with 66186 patients) showed that NOACs did not increase the risk of infection (RR 0.98, 95%CI: 0.96 to 1.01; I^2=0%) (Figure 33)

Post-surgery/wound infection risk was not increased with NOACs with a RR 0.93 (95%CI: 0.59 to 1.46; I^2=0%) in a meta-analysis with 5 RCTs with 14196 patients (Figure 33).

Unexpectedly, NOACs showed a significant 6% risk reduction of urinary tract infection rate (RR 0.94, 95%CI: 0.88 to 0.999; I^2=15%) in a meta-analysis with 78998 patients enrolled with 5 trials (Figure 33). The NNT to prevent one patient to have urinary tract infection with NOACs was 281 (95%CI: 140.6 to >1000000), and 4 events (95%CI: 0 to 7.1) prevented for each 1000 patients treated with NOACs, according to the presented data.

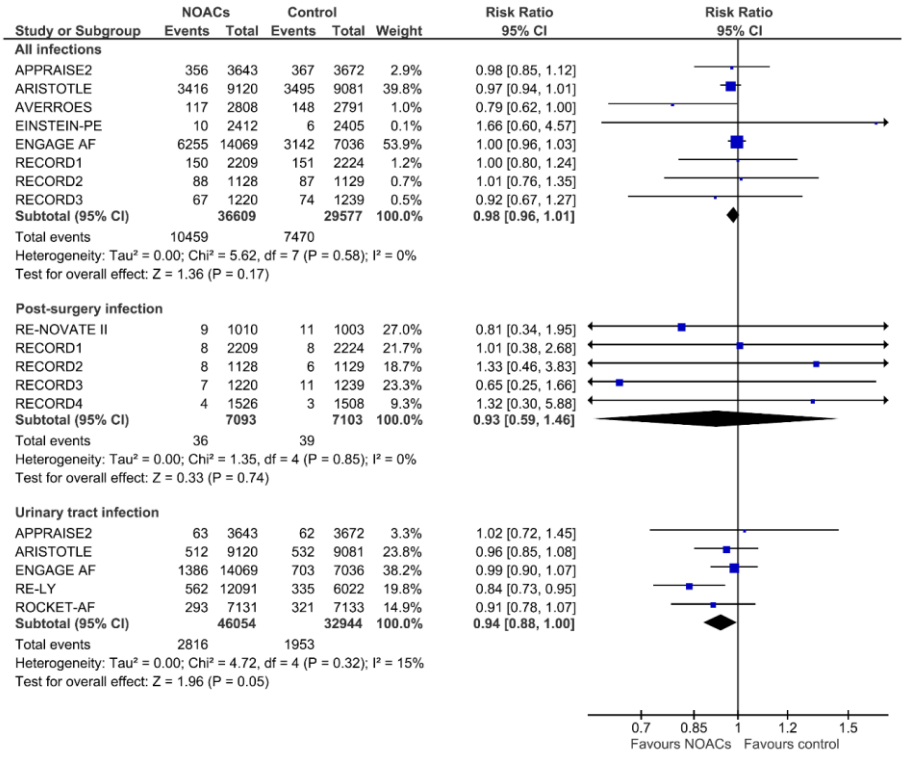

Figure 33: Forest plot with pooled risks of all infections, post-surgery infection and urinary tract infection with NOACs.

Each of the NOACs was individually assessed and none was associated with an increased risk of infection (Figure 34).

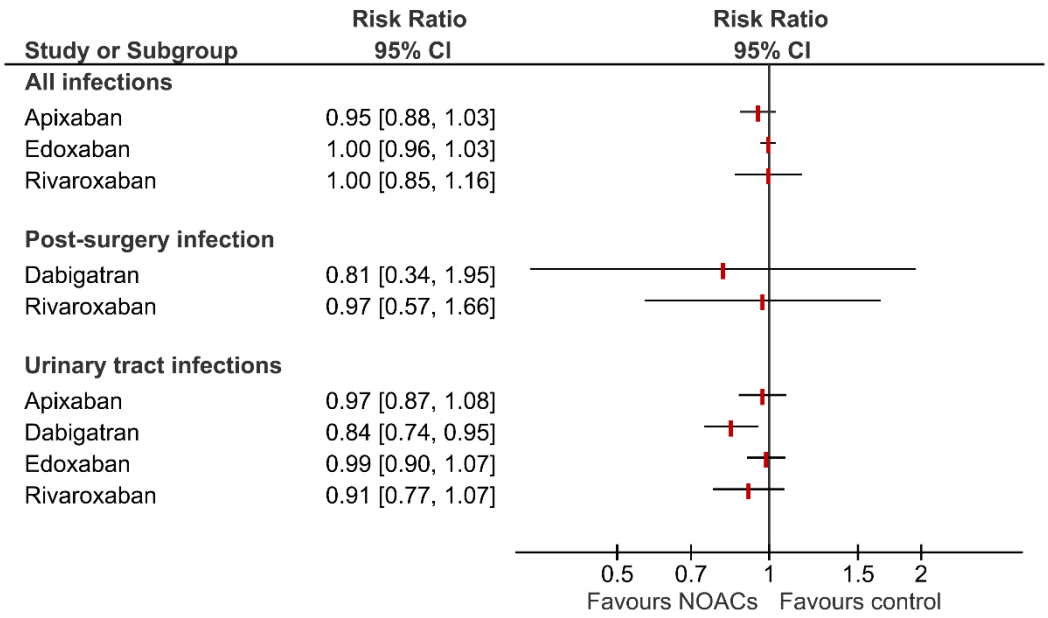

Figure 34: Pooled risks of infections associated to each NOAC.

CONCLUSIONS

Despite the potential link between anticoagulants and immunity, this systematic review did not find any association between NOACs and increased risks of overall infection or post-orthopedic surgery. Conversely, NOACs showed to reduce significantly the risk of urinary tract infections, mostly due to the results of dabigatran in RE-LY trial[70]. Even with this dimension of the sample size, none of the trials were not designed to assess the infectious risk of interventions. Accordingly, the putative 'protective' effect is very small, and it is not warranted. Furthermore, this analysis is limited by the selective reporting bias (opportunistic reporting of infectious adverse events) as the outcomes were not predefined. Pooling the results at study-level also increases the risk of bias particularly when different populations are included in the analysis.

3.4. Acceptability and tolerability

BACKGROUND

The success and effectiveness of any chronic treatment, anticoagulation included, depends on patients' tolerability and adherence to the medication. While venous thromboembolism treatment or prevention may require only temporary anticoagulant treatment [89,90], stroke prevention in AF demands life-long treatment.

NOACs have overcome many limitations of VKAs, namely the variability in dose response and the convenience related to absence of frequent coagulation monitoring and dose adjustments.

However, life-long potential clinical benefits seen in RCTs and meta-analysis are only outweighed if the adverse reactions' and medication adherence profile are at least similar to that experienced by patients treated with VKAs. In this systematic review, tolerability and acceptability of NOACs in patients with AF was assessed, as these patients require long-term (life-long) anticoagulation.

METHODS

This was a systematic review and meta-analysis of randomized controlled trials (full methodology detailed the published version of the article and briefly explained in the Section 3.1) comparing NOACs and VKA in patients with AF.

The outcomes of interest were tolerability and acceptability of NOACs.

Tolerability was indirectly evaluated by determining the incidence of any serious adverse event (SAE), as reported by investigators and/or adjudicated by committees. Whenever possible, treatment-emergent SAEs were retrieved.

Acceptability was split in drug-related (also associated to the tolerability profile) and patient-related treatment discontinuation[97]. Discontinuations due to adverse events were considered to be drug-related, and discontinuations due to patients' own decisions (consent withdrawal and treatment discontinuation) were considered to be patient-related. Whenever possible, the denominator of these outcomes was the safety population of each arm (i.e. patients that took the drug).

Due to the expectation of inclusion of both open-label and blinded RCTs, and considering the possible influence of these characteristics in the analysed outcomes, a prespecified sub-group analysis according to the blinding status of included trials was planned[170]. Despite the distinctive pharmacokinetic and pharmacodynamic properties of individual NOAC drugs, it was hypothesized that these drugs could have a class effect compared to VKAs.

RESULTS

Five RCTs were included in the systematic review evaluating four NOACs[70,109-112]: apixaban[109], dabigatran[70], edoxaban[112], and rivaroxaban (two studies with rivaroxaban[110,111]).

Altogether, these trials enrolled 72 720 patients with AF under oral anticoagulant treatment, 59% of them treated with NOACs. All trials had a double-blinded scheme with the exception of RE-LY which had an open-label design[70].

Tolerability and acceptability analysis

NOACs were associated with a small yet significant 4% risk reduction of SAE in patients with NVAF (RR 0.96; 95%CI: 0.94 to 0.98; Figure 35 upper panel). The results were consistent across studies, without any statistical heterogeneity (I^2=0%). NNT with NOACs to expect the prevention of 1 SAE compared to VKA was 74 (95%CI: 49 to 148) for an average period of 1.7 years. For each 1000 patients treated with NOACs instead of VKA, it is expected that 14 SAE (95%CI: 7 to 20) would be prevented for an average period of 1.7 years.

Drug discontinuation rate due to adverse events was similar between NOACs and VKAs (RR 1.03; 95%CI: 0.88 to 1.21; Figure 35 mid panel). This analysis was remarkable for significant statistical heterogeneity (I^2=93%)

Patient-related drug discontinuation was also similar between NOACs and VKAs (RR 0.99; 95%CI: 0.89 to 1.10; Figure 35 bottom panel), again showing significant statistical heterogeneity (I^2=75%).

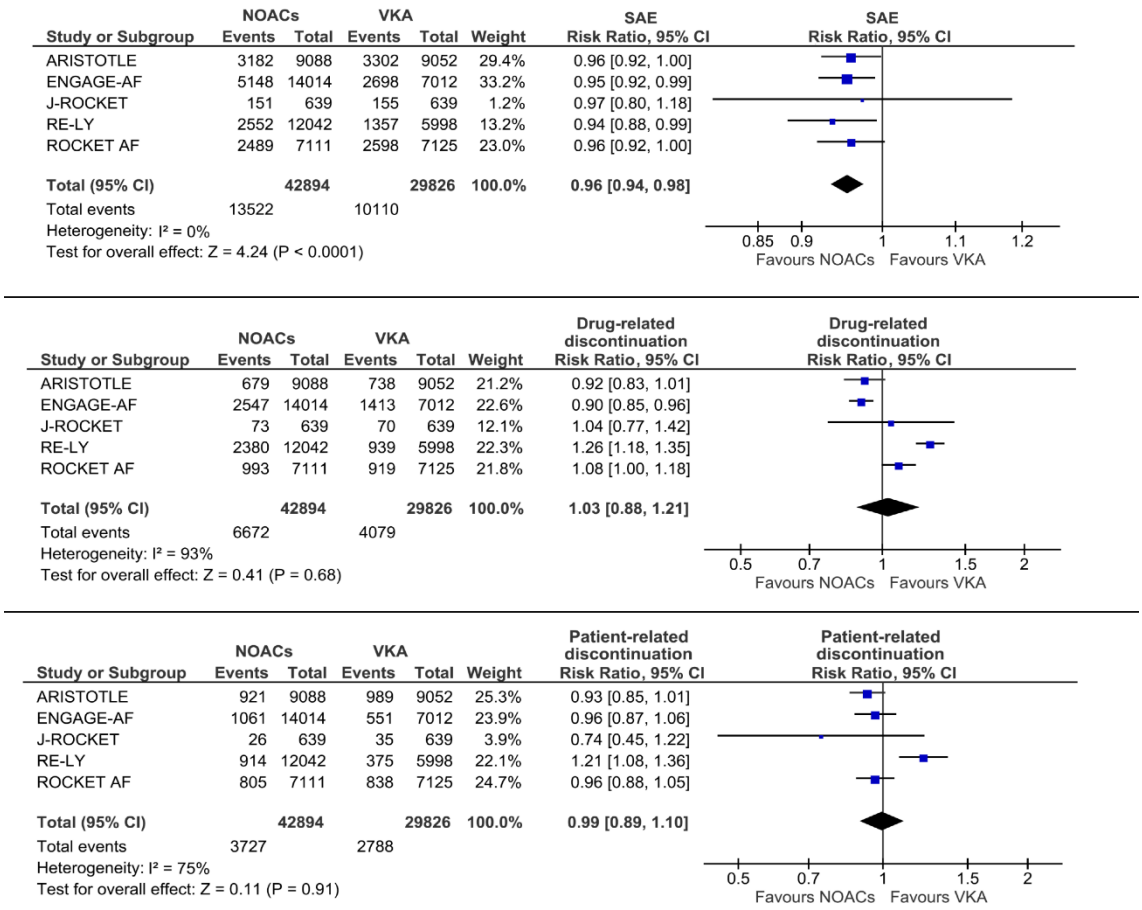

Figure 35: Forest plots with NOACs pooled risks of SAE (upper panel), drug-related discontinuation (mid panel), and patient-related discontinuation (bottom panel).

Subgroup analysis according to study design

RE-LY study (dabigatran *versus* VKA) was the only open-label trial[70]. The risk reduction of SAE was not different between blinded and open-label RCTs (p=0.49) (Figure 36).

For both drug- and patient-related treatment discontinuations, the results for dabigatran *versus* VKA (derived from the open-label RE-LY trial) were significantly different compared to the pooled results for the other NOACs (p<0.0001 and p=0.0001, respectively) (Figure 36).

Dabigatran was associated with a significant increase of both drug- and patient-related treatment discontinuations, while pooled results for the other NOACs showed a reduction in the risk of discontinuation due to patients' own decisions (Figure 36). The level of heterogeneity in pooled estimates for discontinuation due to drug- and patient-related causes decreased when RE-LY trial was removed from the analysis (I^2=67% and I^2=0%, respectively).

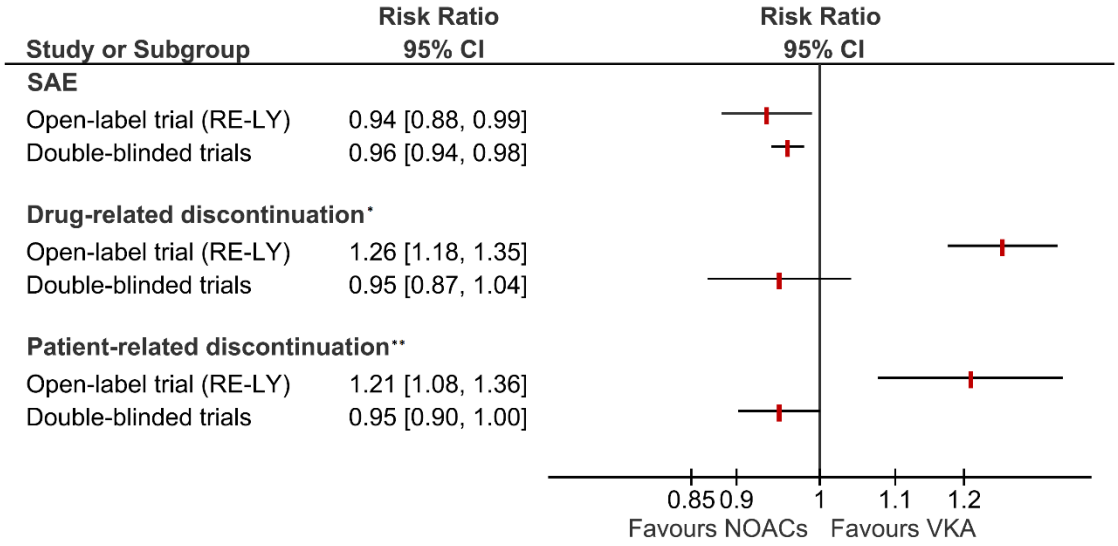

Figure 36: Pooled risks of tolerability and acceptability outcomes according to the trials design (open-label vs. double-blinded). * p-value for interaction <0.0001; ** p-value for interaction =0.0001.

A further exploratory analysis was performed by adding both drug- and patient-related treatment discontinuations into a single outcome. As expected, overall NOACs did not reduce the incidence of this outcome (RR 1.00; 95%CI: 0.88 to 1.14; data not shown in the figures), with high heterogeneity (I^2=95%), mostly due to RE-LY (RR 1.25; 95%CI: 1.18 to 1.32). Without RE-LY, NOACs showed a 5% reduction of drug discontinuation risk (RR 0.95; 95%CI: 0.90 to 1.00; I^2=57%).

CONCLUSIONS

Overall, NOACs were associated with a significant 4% reduction in the risk of SAE. NOACs' drug-related and patient-related acceptability profiles were similar to VKA. At this level NOACs did not show a clear drug-class effect.

3.5. Chapter discussion and conclusions

NOACs have been proven to be at least as efficacious as other alternative treatment options, in particular VKA, with a more favorable pharmacological profile. As seen the number of patients treated with NOACs is increasing overtime.

In this chapter the safety and tolerability profiles of NOACs were evaluated. The main findings were:

1) NOACs have a favorable safety profile with decreased risk of major bleeding, bleeding-related mortality and ICH;
2) NOACs are not more frequently associated with non-bleeding adverse events (including hepatic and renal function).
3) NOACs have a favorable tolerability profile, with a decreased risk of overall serious adverse events and patient-related drug discontinuation (except for dabigatran).

Bleeding adverse events

According to findings presented in this dissertation, NOACs were not associated with an increased risk of major bleeding, or bleeding-related mortality. In fact, based on published random controlled data, NOACs decrease the risk of fatal events directly or indirectly related to major bleeding, particularly in AF patients.

Concerns have been raised against NOACs due to the absence of an antidote to reverse anticoagulation in patients with major bleeding events[171]. In an individual patient the lack of an antidote may interfere with the clinician's perception of available therapeutic rescue options. However, most of the studies show that the majority of major bleeding events are managed solely with supportive therapy or red cell transfusion[70,121,122]. Putting all data into context, NOACs appear to be safer than VKA, even in the absence of specific antidotes for these drugs.

Some of these findings may be tightly related to the decreased risk of ICH with NOACs in patients with AF and VTE requiring medium or long-term effective anticoagulation. Taking into consideration that ICH is commonly associated with important disability and mortality, these results are of paramount importance. Also according to the presented findings, the safer risk profile of NOACs also applies to other conditions with other

standard comparators, such as patients requiring anticoagulation after hip or knee arthroplasty usually treated with LMWH [79].

It is not well established the reason for this safer profile, however it is known that cerebral vessels hemostasis is likely to be highly dependent on the tissue factor/factor VIIa interaction to primarily initiate the coagulation process[172]. Unlike VKA, which block the carboxylation process and inhibit the production of functional factor VII, among other coagulation factors, NOACs directly and selectively inhibit factors IIa or Xa without interfering with the primary hemostatic mechanism of cerebral vessels[172].

As for GI bleeding risk, it is known that to NOACs have an oral route of administration and, with the exception of dabigatran, all of them may have their anticoagulant effect directly in the mucosa of the gut. Dabigatran etexilate is a prodrug, and is converted into the active metabolite by esterases present in the gut, plasma and liver.[173] Moreover, dabigatran's oral route bioavailability is 7% and the remainder may act locally in the absorption site. Therefore it is not surprising that overall NOACs encompass an increased risk of GI bleeding,[125] but these data shows that this increased risk is not due to severe events (major bleeding).

NOACs also did not increased the risk of pericardial and intraocular bleeding, which are important causes of bleeding-related mortality and disability, respectively.

Despite these encouraging safety results, the prescription act of any antithrombotic drug is the net result of balancing the risk of ischemic and hemorrhagic events for an individual patient. Unfortunately, clinical trials still have no standardized measures for net clinical benefit evaluation[174].

Non-bleeding adverse events

Ximelagatran, the first approved NOAC, was later withdrawn from the market in 2004 following the detection of an increased risk of severe liver injury[51]. The hepatic risk profile of this drug was not noticed in short term studies (i.e. less than one month of follow up). In long term trials, the increase in serum levels of ALT (> 3x ULN) was 7-fold higher with ximelagatran compared to warfarin.

This prompted the attention of pharmacovigilance among the newer NOACs studies in respect to hepatic events.

Due to the potential severity of this adverse event it is important to estimate the risk of DILI in the most possible precise way and as soon as possible during the early phase of drug development and before massive post-marketing use. The resuls were robust in terms

of cumulative sample size and follow-up, and failed to find an increased risk of liver injury with NOACs.

Unexpectedly, NOACs in general, and dabigatran in particular (which is not metabolized in the liver), were also less likely to increase transaminases compared to controls. Interestingly, this putative "protective" effect of NOACs was more evident in studies which had as control group LMWH. Therefore, one can hypothesize that these results are not due to a true "protective" effect of NOAC, but rather due to LMWH-associated hepatotoxicity. In fact, hepatotoxicity has been reported to occur in up to 5-10% of LMWH-treated patients[175]. Despite all, it is unlikely that these results have clinical significance and, therefore, no claims can be made to change the current clinical practice based on these results. Furthermore, there were no differences between NOAC and LMWH regarding the elevation of transaminases and bilirubin, which is a more sensitive measurement of DILI risk.

Overall, NOACs were also not associated with an increased risk of renal failure compared to VKA, particularly serious acute renal failure, although some studies reported a higher incidence of creatinine increase with rivaroxaban[176].

Darexaban was another NOAC which have not reached the market[159]. In the pivotal phase III trial, it was with surprise that the risk of insomnia was similar between darexaban and mechanical thromboprophylaxis[160]. Therefore, it was hypothesized that NOACs, as a drug-class, could have an increased risk of insomnia. These findings failed to confirm this hypothesis

As for infection risk, despite the potential link between anticoagulants (particularly those targeting thrombin or Xa, such as NOACs) and immunity, no associations were found between NOACs and the risk of overall infection, post-orthopedic surgery wound infection or urinary tract infection.

Tolerability and acceptability

NOACs were associated with a small, yet clinical significant decrease in the risk of SAE when compared to VKA, without differences between individual NOACs, suggesting a drug-class effect regarding this outcome. These results reflect differences in the tolerability profile, with lower risk of events with NOACs.

Acceptability analysis (whether drug-related or patient-related) returned heterogeneous results. In terms of drug-related discontinuation, and with the exception of dabigatran, NOACs showed an acceptability overlapping that of VKA. In RE-LY study, patients treated with dabigatran had higher discontinuation rates. The knowledge about the treatment assigned in RE-LY can, at least partially, explain these findings because patients who know that they are being treated with a new active drug may be more prone to discontinue in the setting of an adverse event. However, the discontinuation rate in dabigatran group due to adverse events was also significantly higher compared to standard anticoagulation in the double-blinded double-dummy RE-COVER trial that enrolled patients with VTE [113]. Gastrointestinal symptoms, namely dyspepsia, were the main reason for premature dabigatran discontinuation.

Concerning patient-related discontinuation (acceptability), no differences were found between NOACs and VKA. However, excluding the RE-LY trial from analysis because of the above mentioned reasons (open-label design) resulted in a small, yet significant reduction of patient-related discontinuation risk with NOACs. It should be empathized that there are no obvious reasons for the higher rate of patient-related discontinuation among dabigatran-treated patients. In fact, data from RE-COVER trial (double-blind design) on patients with VTE does not support it[113].

It is worth noting that, according to previous publications, drug discontinuation or switch (particularly from NOACs to other options) carries an increased risk of thromboembolic events[174,177].

Limitations

Systematic reviews with meta-analysis are limited by methodological issues associated to meta-analysis and individual studies. The results of the meta-analyses were based on study-level data and not on individual patients' data.

Included studies were powered for their primary outcomes and not to detect differences with respect to most of outcomes evaluated individually. Data here presented were derived from secondary outcomes of included trials and most of them were of very low frequency.

The analyses included a wide range of conditions, however these findings are mostly valid for patients with non-valvular AF potentially suitable for VKA as these were included in all analyses (bleeding events, non-bleeding events, tolerability and acceptability). Patients with valvular AF (particularly significant mitral stenosis and mechanical heart valves) were not

included in any of the studies considered [40]. Patients with non-valvular AF unsuitable for VKA were only analysed in the AVERROES trial (apixaban *versus* acetylsalicylic acid) and considered for evaluation in non-bleeding adverse events only [39]. Despite the differences in the clinical characteristics of AF and VTE patients, data from trials including these conditions were pooled together in bleeding risk evaluation, based on the assumption that the relative risk of interventions would not be different among the diverse prothrombotic diseases using the same control[127]. For non-bleeding risk events, the analysis was performed irrespectively of the conditions and controls, as none of these were deemed to influence the outcomes.

NOACs are a group of anticoagulant drugs composed by oral thrombin and Xa inhibitors. The objective was to evaluate the overall drug-related harms of NOACs, and therefore drugs such as dabigatran and edoxaban were evaluated irrespectively of their higher or lower dose (data were merged). Despite the pharmacodynamic and pharmacokinetic differences among NOACs, these drugs were analysed together under the assumption of a class effect due to NOACs similarities in opposition to VKA, particularly, in bleeding adverse events, tolerability and acceptability.

At outcome level, all bleeding events were pre-defined in the included trials and followed the ISTH definition. However, there is a risk of selective reporting bias for major bleeding case-fatality outcome because NOACs and VKA bleeders have different clinical characteristics and pooled data were not adjusted to those and other possible differences.
Hepatic safety data were mainly based on laboratorial results. To be more accurate, other causes of hepatic injury and cholestasis should also be evaluated, but data were too scarce.
Renal safety, insomnia, and infections data were essentially based on the subjective report of these events by investigators. None of the outcomes were pre-defined, comprehensively searched, or independently adjudicated. Therefore, potential selective reporting bias should be considered.
Nevertheless, and despite these limitations, the results are reasoned to be robust enough to support the conclusions about the safety and tolerability of NOACs.

CONCLUSIONS

In the pooled safety data from phase III RCTs, NOACs were associated with a decreased risk of major bleeding, fatal bleeding and ICH compared to the AVK. Regarding the risk of major gastrointestinal bleeding, intraocular and pericardial, there was no significant increase in these events.

The NOACs are not associated with liver injury or severe renal impairment. Similarly, there was no increased risk of infections or insomnia.

The overall risk of serious adverse events was significantly decreased by NOACs compared to VKA. The results for acceptability (drug discontinuation) were heterogeneous. However, for most NOACs the risk of treatment discontinuation due to drugs-related or patient-related reasons were not increased compared to the VKA in AF patients.

Chapter IV

Pharmacovigilance of oral anticoagulants

4.1. Oral anticoagulants data from the national pharmacovigilance database of spontaneous reports.

INTRODUCTION

In the last years many changes have been observed in the management of prothrombotic conditions due to the arrival of new antithrombotic drugs[178,179]. The already marketed new oral anticoagulants or Non-vitamin K antagonist oral anticoagulants (NOACs) (apixaban, dabigatran, edoxaban and rivaroxaban) showed to be at least as efficacious as Vitamin K Antagonists (VKA) for the prevention of stroke and systemic embolism associated to non-valvular atrial fibrillation and for the treatment of venous thromboembolism (VTE). These drugs were also effective in the prevention of VTE in patients with hip or knee arthroplasty[179].
Clinical trials are majorly designed for efficacy evaluation. The reduced exposure of new drugs during clinical trials before marketing may result in the arising of some unknown adverse drug reactions (ADRs) during the post marketing phase. The knowledge of treatments harms is essential in order to improve the practice towards an effective and safer level. Thus post-marketing drug safety surveillance should complement safety evaluations from clinical trials.
Hereby, the frequency of reported manifestations of ADRs associated to all oral anticoagulants was assessed, using the Portuguese spontaneous reporting database of pharmacovigilance.

METHODS

This observational pharmacovigilance study had a retrospective design and evaluated the spontaneous notifications of adverse events in the Portuguese National Competent Authority Pharmacovigilance Database[180,181].
All oral anticoagulant-related spontaneous notifications of adverse events reported to the pharmacovigilance centres of the Portuguese National Authority of Medicines and Health Products (INFARMED) were assessed. The first NOAC to be commercialized was dabigatran etexilate, in 2010 (according to INFARMED data). Thus, the presented analysis was restricted

to the period of January 2010 to April 2015, for the three available NOACs – apixaban, dabigatran and rivaroxaban[182].

The incidence of anticoagulant-related ADRs, based on the spontaneous notifications, was estimated using nationwide exposures as counting units (CU) and the defined daily dose (DDD) of anticoagulants according to the World Health Organization[183]. Such data was provided also by the Portuguese National Authority of Medicines and Health Products (INFARMED). The incidences were calculated using ADRs/100 000 CU (national oral anticoagulants sells are at this order of magnitude) and ADRs/million of DDD (national oral anticoagulants sells are at the dozens of millions of DDD).

To be eligible, spontaneous notifications had to report the patients' data (demographics, suspected drugs and adverse events) and the professional group of the reporting person (physician, pharmacist, nurse, other health professional or user)[184].

Oral anticoagulant drugs were searched and characterized according to their World Health Organization (WHO) Anatomical Therapeutic Chemical Code (ATC) Classification System: B01AA03 for warfarin, B01AA07 for acenocoumarol, B01AE07 for dabigatran etexilate, B01AF01 for rivaroxaban, and B01AF02 for apixaban[185]. Warfarin and acenocoumarol (these are the only VKA commercialized in Portugal) were grouped into VKA class. Dabigatran etexilate, rivaroxaban and apixaban were further grouped into NOACs class. Parenteral anticoagulants were excluded from this analysis.

Each report refers to a single ADR case and the whole cases were characterized in terms of age and gender distribution, the concomitant use of other relevant non-anticoagulant drugs, as well as the seriousness of the suspected ADRs. According to criteria present in international guidelines, which are also the ones adopted by the Portuguese System of Pharmacovigilance, serious ADRs are those resulting in death, life-threatening events, requiring inpatient hospitalization or prolongation of existing hospitalization, resulting in persistent or significant disability/incapacity or congenital anomaly/birth defect, or any other medical event deemed to be important due to major clinical consequences and/or due to the requirement of any medical intervention to reverse it[184].

Spontaneous reports contained at least one potential ADR which was considered a suspected ADR. Each event was isolated and classified according to a standardized medical terminology that is used in the Medical Dictionary for Regulatory Activities (MedDRA), version 18.0, under the System Organ Class (SOC) and the Preferred Term (PT) levels, determined by the International Conference of Harmonisation[186].

The suspected ADRs were also analysed according to the PT, SOC and use of anticoagulant drug. Due to the multiaxial properties and classification of MedDRA, thrombotic and bleeding events are distributed along the different SOCs. These outcomes are of special interest for patients treated with oral anticoagulants as they represent absence of efficacy (thrombotic events) and hemorrhagic toxicity (bleeding events). Suspected ADRs were scrutinized and classified by two investigators as thrombotic or hemorrhagic according to the Standardised MedDRA Queries (SMQ) terms. SMQs are validated, standard sets of MedDRA terms, used to support signal detection and monitoring. Broad terms SMQs were used to increase the sensitivity of searches. For thrombotic events, PT terms related to venous thromboembolism were identified using the SMQ "Embolic and thrombotic events, venous" terms, while stroke or systemic embolism, and myocardial infarction were identified and classified using the SMQ "Embolic and thrombotic events, arterial" terms. For bleeding events related with gastrointestinal system all terms included in the SMQ "gastrointestinal haemorrhage" were comprehensively searched. For those related with central nervous system bleeding events the SMQ used was "hemorrhagic central nervous system vascular conditions". For the other bleeding events the SMQ terms "haemorrhage" were appraised.

Potential interactions in the reported hemorrhagic cases were appraised according to the concomitant use of certain drugs, that were searched in the database according to their WHO ATC code: B01AC for antiplatelet drugs, B01AB for heparins, M01A for non-steroidal anti-inflammatory drugs (NSAIDs), N06A and N06C for antidepressants, N03A for anticonvulsant drugs and D06, A01AB, A02BD, A07A, D01, D07C, D09AA, D10AF, G01, P, R02AB, R05X, S01, S02, S03 and J for anti-infective drugs. The use of such medication may increase bleeding proneness, as established in some bleeding risk stratification tools[76,187].

The Microsoft Excel® 2010 software was used for the analysis of data. IBM SPSS Statistics 23 software and R-3.2.2 software were used to perform the statistical tests.

The study was approved by the Ethics Committee Board of the Faculty of Medicine, University of Lisbon.

RESULTS

Oral anticoagulant-related ADRs: absolute number and incidence by yearly sells

From January 2010 to April 2015, 794 suspected ADRs from 270 cases fulfilling the inclusion criteria were retrieved from the Portuguese pharmacovigilance database (Figure 37).

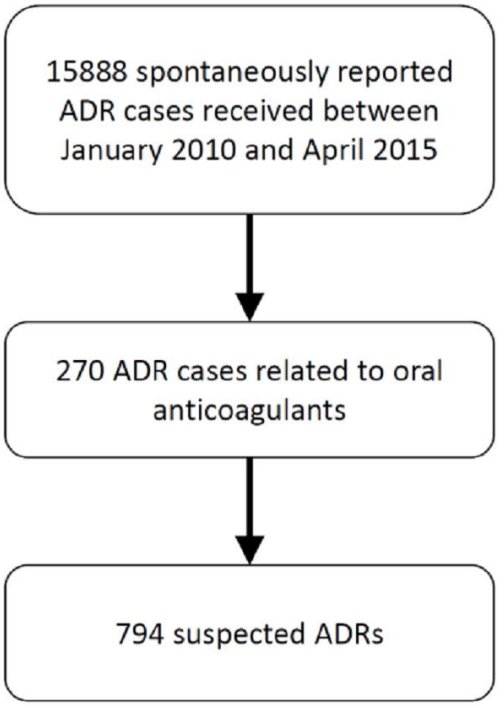

Figure 37: Flowchart of ADR cases and ADRs.

In the period 2010-2014 the yearly number events reported associated with oral anticoagulants increased significantly from 14 to 371 (Figure 38).

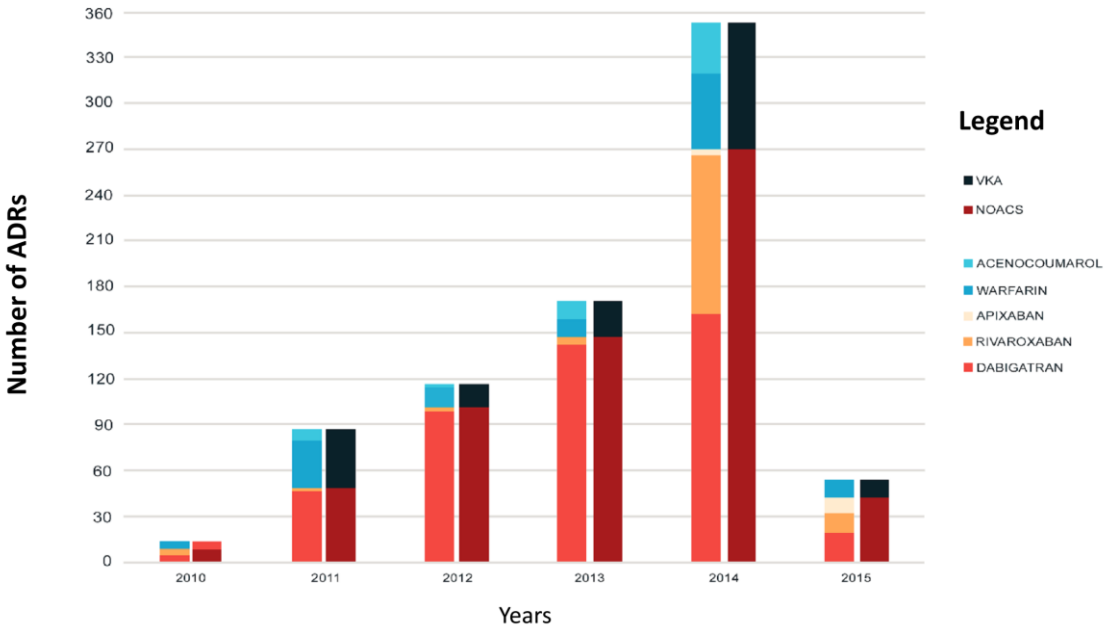

Figure 38: Absolute number of ADRs according to the oral anticoagulant from January 2010 until April 2015.

However, the incidence according to drugs exposure had a peak in 2012 (19 ADRs per million of DDD, and 61 ADRs per 100 000 CU) mostly due to reports of events related to NOACs. NOACs had then 400 spontaneously reported ADRs per 100 000 of CU (Figure 39A), and 145 ADRs per million of DDD (Figure 39B). The following years showed a decrease of the reporting incidence related to overall oral anticoagulants and NOACs. The incidence VKA-related spontaneously reported ADRs was low but their peak was reached in the year 2014 and the first four months of 2015 (12 ADRs per 100 000 CU, and 4 ADRs per million of DDD) (Figure 39).

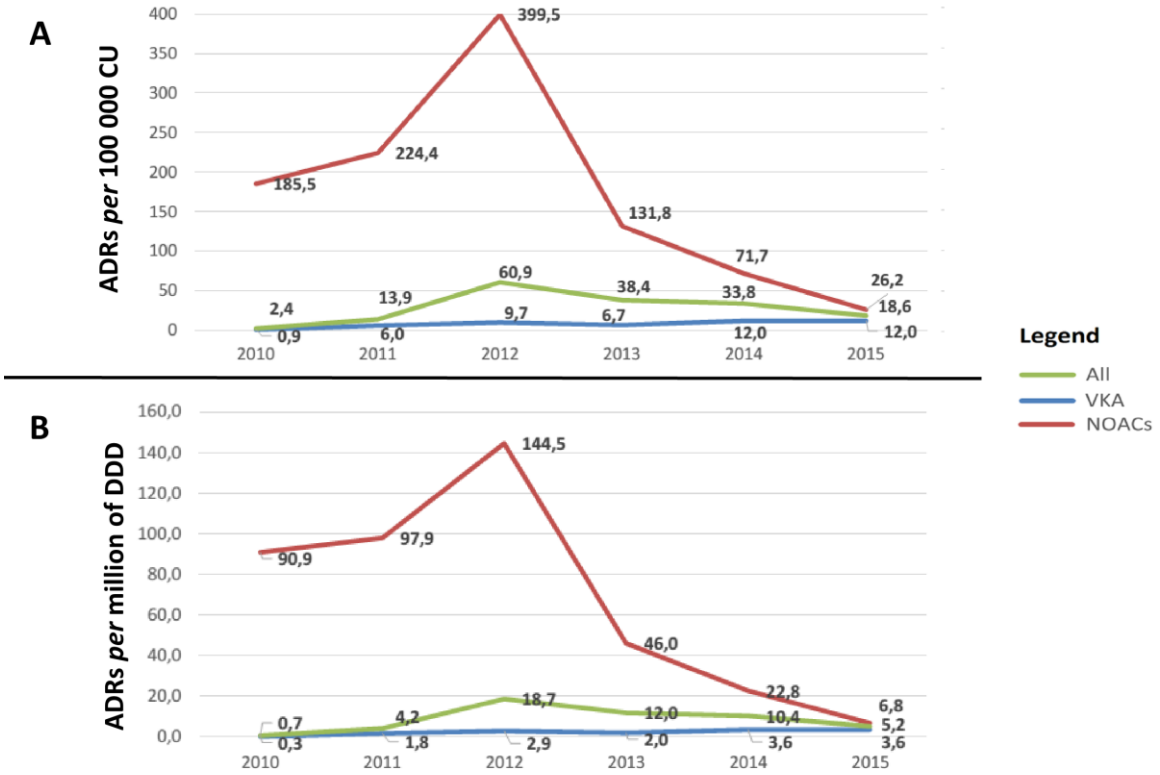

Figure 39: The yearly incidence of ADRs related to all oral anticoagulants (green solid line), VKA (blue solid line), and NOACs (red solid line) per 100 000 CU and million of DDD.

Overall characterization of patients, ADRs, and notifiers.

About 96% of the suspected ADRs (764 events) complied with seriousness criteria, and 13% of the patients (35 patients) had a lethal outcome. Overall, NOACs (apixaban, dabigatran and rivaroxaban) were suspected to be related to 78% of the oral anticoagulants ADRs. The remaining ADRs (22%) were related to VKAs (Table 13).

Table 13: Characteristics of patients, notifiers and suspected ADRs.

	Overall	*VKA*	*NOACs*
Patients			
n (%)	271	62 (23%)	209 (77%)
Mean age	71	71	71
Male (% in each group)	125* (46%)	32 (52%)	92 (44%)
Lethal events (%)	35 (13%)	5 (8%)	30 (14%)
Suspected ADRs			
N	794	174**	622**
Seriousness	763	159**	606**
Notifier body			
Physician	539 (67,5%)	50 (32,1%)	456 (74,9%)
Pharmacist	141 (17,7%)	73 (46,8%)	68 (11,2%)
Nurse	1 (0,1%)	1 (0,6%)	0 (0,0%)
Patient or other non-healthcare professional	31 (3,9%)	0 (0,0%)	31 (4,9%)
Dentist	67 (8,4%)	32 (20,5%)	35 (5,7%)
Others	19 (2,4%)	0 (0,0%)	19 (3,1%)

NOACs, non-vitamin K antagonist oral anticoagulants; *VKA*, vitamin K antagonists.

*No data for some ADRs

**There are two ADRs related to patients that were exposed to both VKA and NOACs

The mean age of patients with reported adverse events was 71 years old. There were not any significant differences between NOACs and VKAs, regarding mean age, gender and the proportion of patients with a lethal outcome (Table 13).

Physicians were the professional group that most frequently reported ADRs, accounting for 67.5% of the ADRs. There are 7 patients whose reports were done by 2 or more reporting groups. In VKA group, pharmacists were the top reporting group (46.8 %), while other NOACs ADRs were reported by physicians (74.9 %). It should be emphasized that dentists contribute importantly the VKA ADR reporting (20.5%).

Evaluation of ADRs according SOCs among NOACs and VKA

The evaluation according SOCs showed that the most frequently reported ADRs are associated with "gastrointestinal disorders", "nervous system disorders" and "general disorders and administration site conditions". NOACs had a higher proportion of ADRs reported by SOCs, with the exception of the SOC "Investigations", which was mostly reported in association with VKA. The NOAC responsible for the majority of the cases was expectedly dabigatran because it was the first NOAC commercialized. The VKA with more notifications is warfarin, which can be explained by its widespread use in Portugal compared with acenocoumarol. Figure 40 depicts the absolute number of ADRs stratified oral anticoagulant class and according to each SOC.

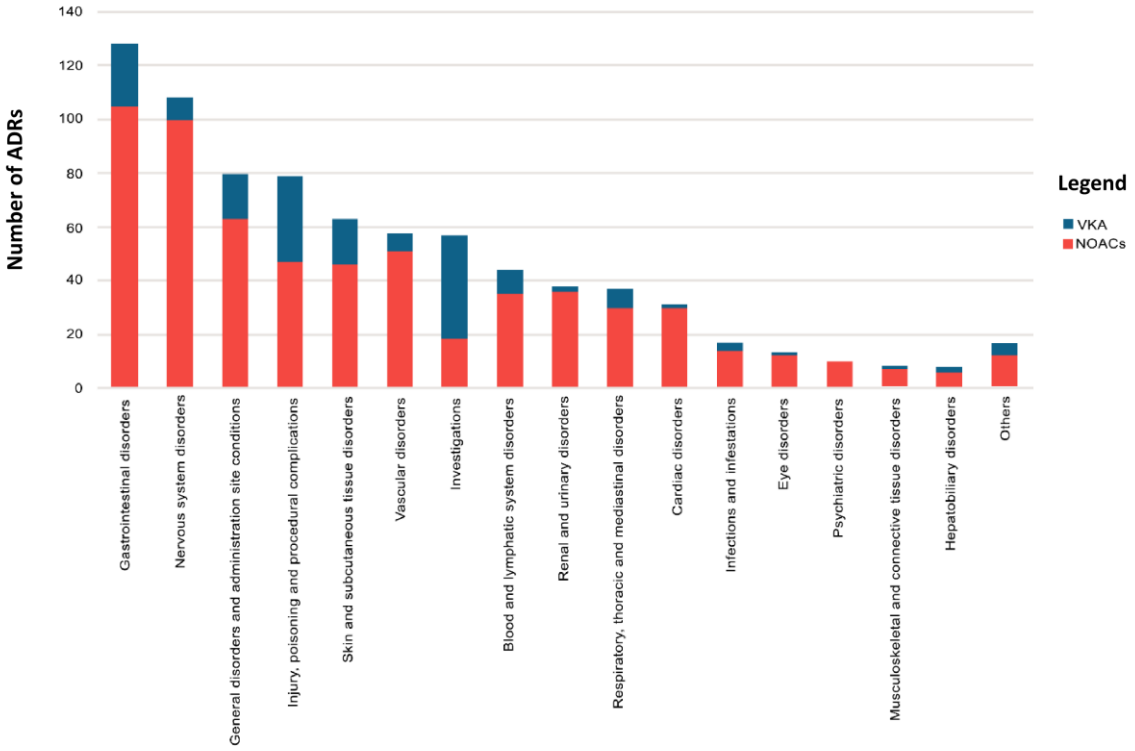

Figure 40: Proportion of suspected ADRs associated to oral anticoagulants according to SOC.

Evaluation of thromboembolic and hemorrhagic ADRs among NOACs and VKA

Aggregating ADR data into clinically meaningful SMQs, 49 arterial thromboembolic events, 13 venous thromboembolic events, and 200 hemorrhagic events were reported.

Among the reported 63 thromboembolic events (there was one case of atrial thrombosis that did not allow to classify as arterial or venous thromboembolism), 60 of these occurred with

NOACs (95%). The reported proportion of arterial or venous thromboembolic events (among the ADRs of the same drug class) was numerically higher with NOACs (Table 14). Considering all the reported hemorrhagic events, 84% (168 events) arose with NOACs, and the relative proportion of reported hemorrhagic events (either global, gastrointestinal or intracranial hemorrhages) according to each drug class among the global ADRs was numerically higher with NOACs (Table 14). The 57 GI hemorrhagic events associated with NOAC represented 54% of the NOACs Gastrointestinal (SOC) ADRs (57 of 105), and 51 of these events were reported with dabigatran.

Table 14: ADRs classified according to SMQ terms.

ADRs	***VKA***	***NOACs***
Arterial thromboembolism (SMQ)*	3 (1,7%)	46 (7,4%)
Venous thromboembolism (SMQ)*	0 (0,0%)	13 (2,1%)
Hemorrhage (SMQ)	32 (18,4%)	168 (27,0%)
Gastrointestinal hemorrhage (SMQ)	10 (5,7%)	57 (9,2%)
Intracranial hemorrhage (SMQ)	2 (1,1%)	22 (3,5%)
Other hemorrhages	20 (11,5%)	89 (14,3%)

Percentages are expressed as proportion of SMQ among all ADRs with the same drug class.

NOACs, non-vitamin K antagonist oral anticoagulants; *PT*, preferred term; *SMQ*, Standardised MedDRA Queries; *VKA*, vitamin K antagonists.

*There was one case of atrial thrombosis that was not classified in any of these SMQs.

The concomitant use of oral anticoagulants with other drugs known to increase the hemorrhagic risk (heparins, NSAIDs, and antiplatelet drugs) corresponded solely to 11% of the hemorrhagic reports (Figure 41). Yet among VKA-reported hemorrhagic events, about 30% took concomitantly other relevant drugs, specially heparins (17%) or NSAIDs (9%) (Figure 41). Concerning NOACs-reported hemorrhagic events only 5% used other drugs that increase the bleeding risk (Figure 41). There were no bleeding events reported in patients exposed concomitantly to oral anticoagulants and anticonvulsants, antidepressants or anti-infective drugs.

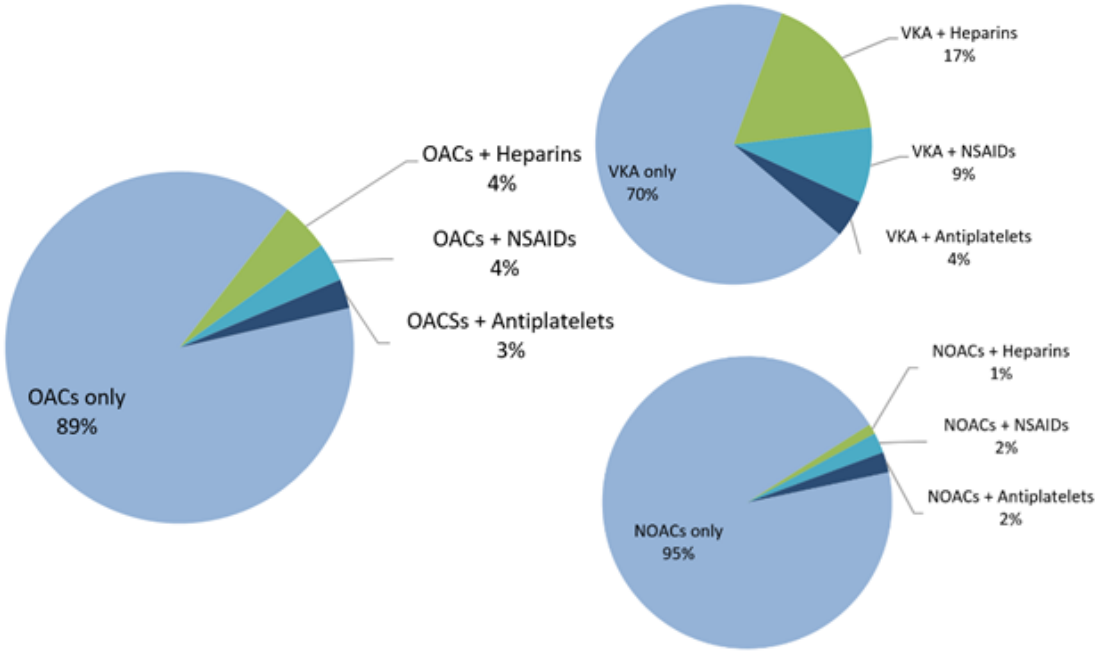

Figure 41: Proportion of concomitant use of heparin, NSAID and antiplatelet drugs in the reported hemorrhagic events. NSAIDs: Non-steroidal anti-inflammatory drugs; NOACs: non-vitamin K antagonist oral anticoagulants; OACs: Oral anticoagulants.

Evaluation of ADRs by PT terms

Looking individually to drugs and ADRs by PT terms, most of the reported events associated to NOACs were related to the ineffectiveness of oral anticoagulants (Table 15). Ischemic stroke was the most reported event related to the use of dabigatran while for rivaroxaban the most frequent suspected ADR was deep vein thrombosis. On the other hand, the adverse events related to the use of VKA are mostly associated to abnormal laboratorial values (Table 15).

Table 15: The most frequent suspected ADRs by PT terms according to each oral anticoagulant class and drug.

Drug	*MedDRA PT term*	*Frequency*
VKA	International normalized ratio increased	31
	Drug monitoring procedure incorrectly performed	20
	Drug interaction	7
	Dermatitis acneiform	5
	Thrombocytopenia	5
NOACs	Ischemic stroke	29
	Anemia	22
	Gastrointestinal hemorrhage	11
	Hematochezia	11
	Rectal hemorrhage	10
Warfarin	International normalized ratio increased	22
	Drug monitoring procedure incorrectly performed	11
	Thrombocytopenia	5
	Dermatitis acneiform	5
	Drug interaction	5
Acenocoumarol	Drug monitoring procedure incorrectly performed	9
	International normalized ratio increased	9
	Drug ineffective	3
	Drug interaction	2
	Vasculitis	2
Dabigatran	Ischemic stroke	28
	Anemia	19
	Hematochezia	11
	Haemorrhage	10
	Fall	10
Rivaroxaban	Deep vein thrombosis	4
	Rectal haemorrhage	4
	Uterine haemorrhage	3
	Blot blister	3
	Chest pain	3
Apixaban	Somnolence	1
	Platelet count decreased	1
	Fatigue	1
	Gastrointestinal haemorrhage	1
	Epistaxis	1

NOACs, non-vitamin K antagonist oral anticoagulants; *PT*, preferred term; *VKA*, vitamin K antagonists.

DISCUSSION

The study about the oral anticoagulants-related adverse events reported to the Portuguese pharmacovigilance centres concluded that the absolute number of reported events was increasing, and that ADRs reports were more often associated with NOACs than with VKA, reflecting their novelty. The reporting incidence peak (taking into account the annual sell of CU and DDD) was in 2012. Since 2012 the incidence of NOACs-related ADRs has been decreasing. Both increased experience with NOACs and the increasing scientific evidence about key outcomes in patients treated with this class of drugs could have contributed decisively. Physicians were the healthcare professionals that most frequently notified adverse events with NOACs, possibly reflecting the careful and watchfulness of the reporters as prescribers of a new drug.

Dabigatran was the first NOAC to be commercialized, followed rivaroxaban, and more recently apixaban. The timing for commercialization, and thus exposure, largely influenced the proportion of ADRs associated to NOACs: higher with dabigatran, lower with rivaroxaban, an even lower with apixaban. Gastrointestinal (GI) signs/symptoms were the most frequently reported manifestations associated with NOAC (16.9%) with 9.2% of NOACs ADRs being related to GI bleeding. The GI tract is the most common site associated to major bleeding events. NOACs have been associated with increased risk of GI bleeding[125], even though it is known that the increase of bleeding risk is usually not associated with severe events as previously shown (Chapter IV)[188]. Thromboembolic events accounted for almost 10% of the overall NOACs reported ADRs while haemorrhage was responsible for 27% of them. Thromboembolic event reports associated with VKAs accounted for 1.7% while hemorrhages were present in 27% of the ADRs. In randomized controlled trials NOACs were at least as efficacious as VKA concerning stroke and systemic embolism[86]. NOACs were also associated with decreased risks of major bleeding and fatal bleeding[86,189]. Therefore, the differences in the proportions may not reproduce the population incidences of these adverse events but rather reflect the unexpectancy of the reporter of the ADRs regarding these outcomes, considering the best available evidence. Other adverse events previously studied, such as infections or hepatic adverse events[190,191], also showed low proportions in both drug classes. Warfarin and acenocoumarol reported events were mostly based on impaired international normalized ratios (INR) and pharmacists took an important role on reporting. Dabigatran and rivaroxaban's top suspected ADRs were ischemic stroke and deep venous thrombosis, respectively. Despite

the potential risk reduction of these events with NOACs, all RCTs showed that a residual thrombotic risk exists and patients may have thrombotic events in such conditions. It is worth noting that VKAs have their efficacy and safety dependent on keeping the INR into therapeutic ranges. Portugal is a country with overall low percentages of time in therapeutic range with VKA[71,182,192,193], which would preclude high rates of reported ADRs. However, as the act of reporting depends on the sensibility of the notifiers, it is possible that the years of experience with VKA harms incorrectly desensitizes patients and/or healthcare professionals from reporting the ADRs to the pharmacovigilance centres, otherwise, the small number of ADRs found in the present study would be contradictory compared to the data found in RCTs[194]. Even in the presence of a low number of VKA-related ADRs, their incidence (using either CU or DDD exposures) recently reached its maximum. It can be speculated that the licensing of NOACs and the current scientific discussions has increased the watchfulness of the community (particularly pharmacists and nurses, which are healthcare professionals involved in INR measurements) around the safety of these drugs. In the other hand, the nature of the most common ADRs are laboratorial, are expected (do not introduce novelty), and may reflect the standardized procedures of a healthcare professionals' cluster that actively report ADRs.

Limitations

The pharmacovigilance study about the ADR related to oral anticoagulants was limited by the context of spontaneous reporting. It is important to notice that in Portugal the consumers are allowed to report ADR since July 2012. With 62 reports (about 4%) sent by these stakeholders, the number of reported ADRs increased slightly.

Causality, which is an important feature in pharmacovigilance was not reported because an important share of the ADRs did not have this parameter in the database. Therefore, as for any data mining study, the robustness of the conclusions depends on the database completeness, which was reasonable fairly reasonable.

CONCLUSIONS

The incidence of oral anticoagulant-related ADRs, considering the sells by DDD or CU, has reached its peak in 2012 and have been decreasing since then. However, the absolute number of ADR reports associated with oral anticoagulants has increased overtime. The majority of reports and ADRs were related to NOACs. These were usually reported by physicians and involve the GI tract or nervous system manifestations. Among VKA, most of the ADRs were related to laboratorial parameters and pharmacists more frequently reported the ADRs of this class of oral anticoagulants. One quarter of the reported NOACs ADRs were hemorrhagic and 10% were related to thromboembolic events (lack of efficacy). About 20% of VKA ADRs report to hemorrhagic events.

Chapter V

The socio-economic impact of atrial fibrillation and oral anticoagulants

Part of the contents of this chapter were published in:

- Gouveia M, Costa J, Alarcão J, Augusto M, Caldeira D, Pinheiro L, Vaz Carneiro A, Borges M. Burden of disease and cost of illness of atrial fibrillation in Portugal. ***Rev Port Cardiol.*** 2015;34:1-11.

- Costa J, Fiorentino F, Caldeira D, Inês M, Pereira CL, Pinheiro L, Vaz Carneiro A, Borges M, Gouveia M. Cost-effectiveness of the non-vitamin K antagonist oral anticoagulants for Atrial Fibrillation in Portugal. ***Rev Port Cardiol*** 2015;34:723-37

5.1. Burden of disease and cost of atrial fibrillation in Portugal

BACKGROUND

Atrial fibrillation (AF) is the most common sustained arrhythmia. It was estimated in 2010 that 33.5 million individuals worldwide,[195] and nearly nine million individuals in the European Union (EU),[196] had AF; the number in the EU is predicted to double to nearly 18 million by 2060.

Against this background, it is important to assess the economic impact and burden and cost of illness of AF in Portugal, which is the aim of the present study.

The purpose of studies on cost of illness is to measure the impact of a disease or risk factor in terms of use of economic resources and reduction in economic activity due to associated disability. Studies on burden and cost of illness are not strictly speaking economic evaluations, since they do not address specific interventions or compare alternative interventions; rather, they seek to describe accurately the status of a particular health problem and its magnitude.

METHODS

Burden of disease

Burden of disease is estimated by means of disability-adjusted life years (DALYs), a measure of the years of health lost due to disease or premature death. It includes two time-based indicators: years of life lost, the difference between age at death and standard life expectancy for that age; and years lost due to disability.[197] Disability is assigned a severity weight between 0 (no disability; perfect health) and 1 (total disability or death). These weights were originally defined by expert panels at the World Health Organization (WHO), and were re-estimated for the Global Burden of Disease Study 2010 through a large-scale empirical investigation.[198] The formula used is:

$$DALY = \int_{a}^{a+L} DCxe^{-\beta x}e^{-r(x-a)}dx$$

where:

a – age of onset,

L – duration of disability or time lost due to premature mortality,

D – disability weight (between 0 and 1),

C – age-weighting correction constant (0.04),
e – expectation of life,
x – age (ranging between a and a+L),
¿ – parameter from the age-weighting function (0.1658), and
r – discount rate (3%).

The discount rate used in this calculation is 3%, and the calculation includes different weighting for different age-groups, with the middle age-group (20–50 years), the years when people tend to be raising children, being assigned greater weight.[197]

Whenever direct evidence about the duration of diseases is not available (an information which is needed to calculate DALYs), the DisMod II model (developed by Barendregt et al. for the WHO[199]) was used. This exploits the causal relations between the variables that describe a disease process by age-group and gender: incidence, prevalence, remission, case fatality, mortality, relative risk (RR) for mortality, and duration.

The model was calibrated using data from the Portuguese Institute of Statistics on the resident population and mortality in Portugal for 2010, as well as the findings of the FAMA study (on AF prevalence) and the Rotterdam Study (on AF incidence).[54,200,201] The remission rate of AF was assumed to be zero. It should be mentioned that AF can often be asymptomatic, and that the reported incidence and prevalence may be underestimated.[145,202]

In order to calculate DALYs due to disability, the degree of disability attributable to a given health problem must be specified. The weighting factors used to characterize the relevant conditions in this study were those published in the Global Burden of Disease Study 2010.[198]

The calculations were based on population and mortality statistics from the WHO for 2010, hospital data from 2011 and official NHS prices for 2013. Data on mortality from AF and stroke in Portugal were taken from the WHO's European Detailed Mortality Database (http://data.euro.who.int/dmdb/). Most deaths from stroke in this database are not specified as ischemic or hemorrhagic, so on the basis of the DRGs and in the opinion of the expert panel, it was assumed that 30% in women and 40% in men are hemorrhagic.

Cost of illness

The first step in the analysis was to identify the conditions that are related to AF as well as the disease itself. The main complications of AF are heart failure and ischemic stroke, the latter being the most serious.[203,204] The relation between AF and stroke is unequivocal:

patients with AF have an age-adjusted risk that is five-fold higher than the general population, and stroke in AF patients is more likely to lead to severe disability.[205] With regard to intracranial hemorrhage, the risk is similar to that of the general population, but it is higher in AF patients under anticoagulant therapy.[205,206]

The conditions considered in the analysis were AF and ischemic stroke, identified by the International Classification of Diseases, Ninth Edition, Clinical Modification (ICD 9-CM) codes 427.31 (Atrial fibrillation), 427.32 (Atrial flutter), 433 (Occlusion and stenosis of precerebral arteries [with cerebral infarction]) and 434 (Occlusion of cerebral arteries [with cerebral infarction]).

The second step was to establish the quantitative relation between AF and stroke by estimating the fraction of the cost and burden of stroke that statistically is due to AF, using the epidemiological concepts of RR and population attributable fraction (PAF). RR in this case is the ratio between the risk of suffering stroke in a population with AF and the risk in a population without AF. The values for RR used in this study, taken from Kannel et al.,[207] based on data from the Framingham Study and recently updated by Ball et al-,[208]

The PAF is the proportion of cases that would not occur in a population if the risk factor were eliminated and can be calculated by the equation[209]:

$$PAF = \frac{P(RR-1)}{P(RR-1)+1}$$

where:

- PAF – population attributable fraction,
- P – prevalence of AF, and
- RR – relative risk of patients with AF suffering stroke.

Direct costs attributable to atrial fibrillation

As well as the burden of disease, AF is also responsible for costs to society and to the NHS, considered as direct costs attributable to atrial fibrillation, which in this study are divided between inpatient and outpatient care.

The centrally managed database of diagnosis-related groups (DRGs) of the Portuguese NHS for 2011 was used to estimate resource use for inpatient care, including other interventions covered by the DRGs such as outpatient surgery and day hospital sessions arising from AF and associated conditions.

Hospitalizations were identified on the basis of a primary diagnosis of AF or of ischemic stroke in accordance with the ICD 9-CM.

The unit costs used in the analysis were taken from Order in Council 163/2013, which defines the prices associated with DRGs and other health interventions. The costs of AF- and stroke-related admissions were calculated by summing the product of the number of patients in each DRG and the price of the corresponding DRG.

Outpatient costs include direct medical costs (consultations, emergencies, diagnostic and therapeutic interventions, drugs, physiotherapy sessions, etc.), and direct non-medical costs (urgent and non-urgent patient transportation and institutionalization).

Resource use was estimated on the basis of the literature and on the findings of a panel of experts from various medical specialties convened to define resource use in patients with AF and ischemic stroke.

Indirect costs of atrial fibrillation

In calculating the indirect costs of AF, only costs associated with lost production due to the disease were included (excluding losses due to premature death).

The absenteeism due to ischemic stroke attributable to AF must be taken into account as well as that of AF itself. Calculation of the indirect costs of stroke directly attributable to AF requires use of the PAF. Absenteeism related to AF and ischemic stroke may have different reasons but given the nature of AF, it is only ischemic stroke that leads to prolonged absence from work due to physiotherapy sessions and/or other reasons.

RESULTS

Burden of disease

Disability-adjusted life years due to death

The first step in quantifying the burden of disease arising from mortality attributable to AF is to calculate the number of deaths and DALYs due to diseases associated with AF., and that in 2010 there were 813 deaths from AF (303 men and 510 women) and 9316 deaths from ischemic stroke.

It was estimated that in 2010 33753 DALYs were lost from deaths due to AF and stroke. The burden of stroke attributable to AF in Portugal in 2010 is estimated at 4070 deaths

(3.8% of all deaths) and 10521 DALYs due to death (1.7% of all DALYs from premature death). Figure 42 shows the distribution of deaths for men and for women by age-group.

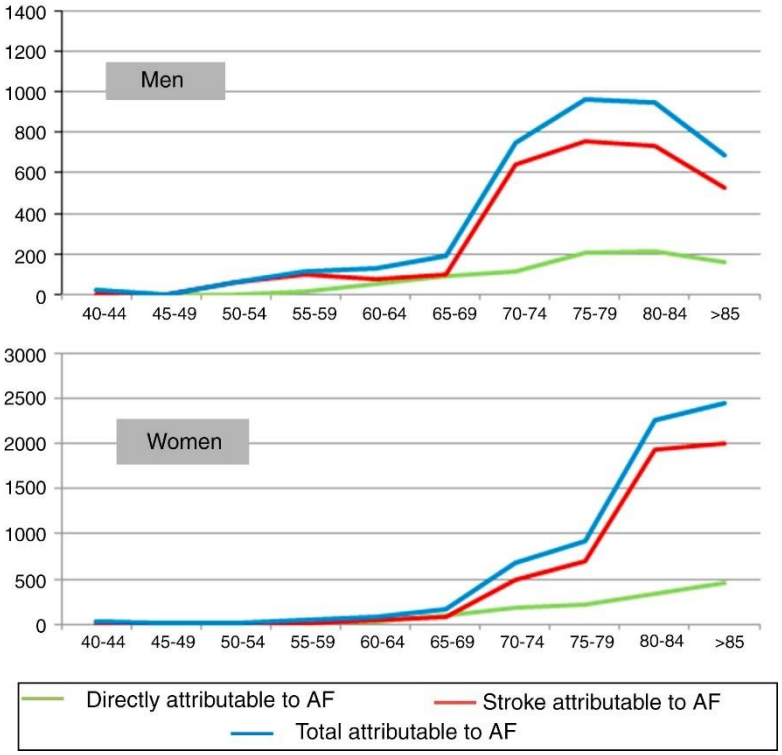

Figure 42: Mortality attributable to atrial fibrillation by age-group and gender. AF: atrial fibrillation.

Figure 43 shows the distribution of DALYs due to death attributable to atrial fibrillation by age-group and gender. Stroke was responsible for the majority of life years lost due to premature death attributable to AF in both sexes.

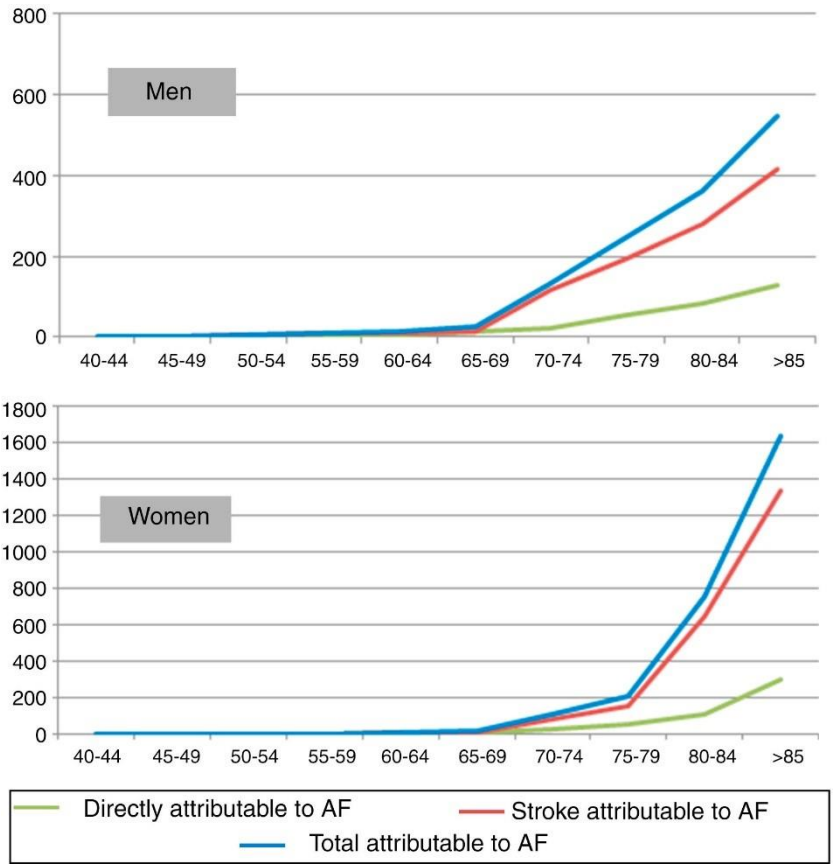

Figure 43: Disability-adjusted life years due to death attributable to atrial fibrillation by age-group and gender. AF: atrial fibrillation.

It can also be seen in Figure 43 that the distribution of burden of disease at more advanced ages differs markedly between men and women, mainly due to differences in the number of men and women in older age-groups. Thus, there are more DALYs due to death attributable to AF per 100000 individuals in men up to the age of 79 (437 vs. 304 for women), but this pattern is reversed over the age of 80 (928 for men vs. 1446 for women).

Disability-adjusted life years due to disability

The severity weight for disability due to AF is 0.145. For stroke, two representative cases – moderately severe stroke with long-term sequelae (weight 0.076) and moderately severe stroke with long-term sequelae and cognitive deficit (weight 0.312) – were considered and the mean of the two (0.194) was adopted for this study.

It is estimated that 14% of AF patients in Portugal have suffered stroke. Calculation of the severity weight in these patients entails adding to the mean weight for AF (0.145) a part of the corresponding disability weight for stroke. The mean RR of stroke for the population with AF is 3.71. The proportion of stroke attributable to AF is (RR-1)/RR, hence the

fraction of strokes in AF patients attributable to AF itself is 73.05%. Considering that 14% of AF patients have suffered stroke, the mean disability weight of AF is (0.145+0.14*0.7305*(0.194−0.145))=0.15. On this basis, AF caused a loss of 12563 DALYs due to disability in 2010, over 5000 for men and over 7000 for women.

Adding DALYs due to premature death and due to disability gives a total burden of disease attributable to AF of 23084 DALYs (Figure 44), of which DALYs due to disability account for around 54%.

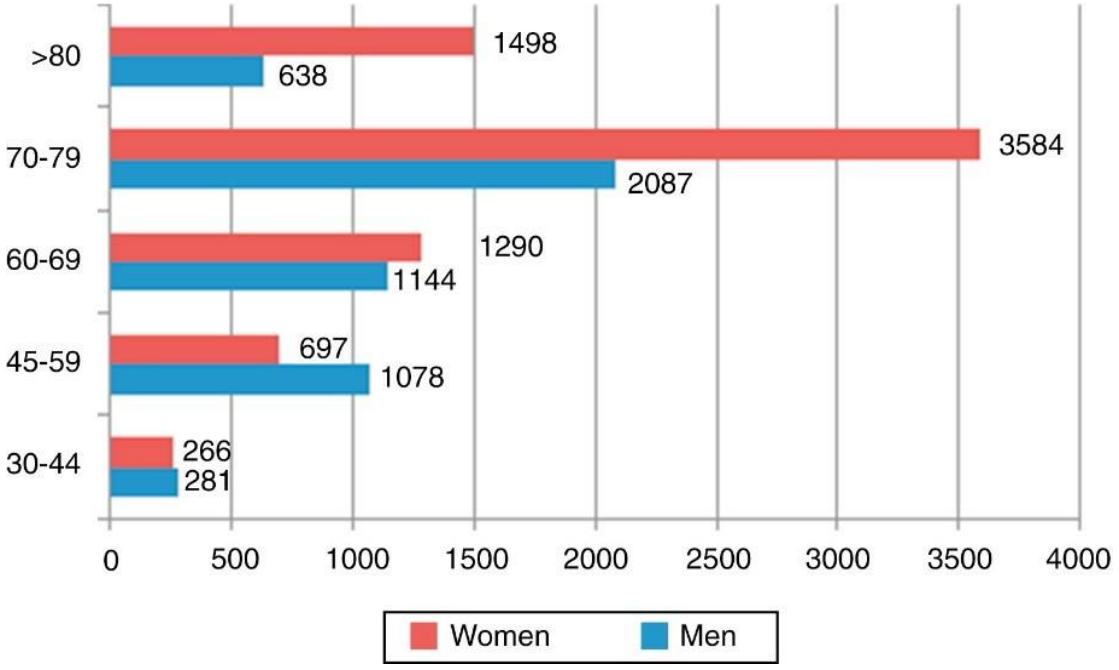

Figure 44: Total disability-adjusted life years attributable to atrial fibrillation by age-group and gender.

Cost of illness

Direct costs

Costs of inpatient care

Table 16 summarizes the total costs of inpatient care attributable to AF. The total cost of inpatient care (including outpatient DRGs) attributable to AF is €34503800. The data shown in Table 16 reveal that the cost of hospitalization for AF itself accounts for 55% of all costs attributable to AF, with ischemic stroke accounting for the remainder.

Table 16: Costs of inpatient care attributable to atrial fibrillation.

Disease	No. of episodes	Total cost (€)	PAF (%)	Attributable cost (€)
Inpatient DRGs				
AF	6339	17569100	100	17569100
Ischemic stroke	20903	113310028	14	15523595
Outpatient DRGs				
AF	259	1410227	100	1410227
Ischemic stroke	4	6409	14	878
Subtotal				
AF	6598	18979327	100	18979327
Ischemic stroke	20907	113316437	14	15524473
Total				34503800

AF: atrial fibrillation; DRG: diagnosis-related group; PAF: population attributable fraction.

Costs of outpatient care

Based on the resource use estimated by the expert panel and on unit costs, the outpatient costs attributable to AF and ischemic stroke were calculated for the year of the diagnosis or event and following years (Table 17). The total cost of outpatient care attributable to AF is around €22 million in the year of the diagnosis or event and €59 million for patients diagnosed in previous years. The outpatient cost attributable to AF accounts for 45.2% of the total costs attributable to AF.

Table 17: Outpatient costs attributable to atrial fibrillation.

	No. of patients		Total cost (€)		
	Incidence-mortality	**Prevalence-(incidence-mortality)**	**Year of diagnosis**	**Patients diagnosed in previous years**	**Total (€)**
AF	10960	72160	7140340	37229346	44369687
Stroke	2171	16097	15185149	21431089	36616238
Total			22325489	58660435	80985925

AF: atrial fibrillation.

The total direct costs attributable to AF are €115.5 million, made up of €34.5 million for inpatient care (Table 16) and €81 million for outpatient care (Table 17). Ischemic stroke is responsible for 45% of all direct costs attributable to AF.

Indirect costs

Indirect costs of atrial fibrillation without stroke

When estimating the indirect costs of AF without stroke it was assumed that the disease's impact is only in terms of absenteeism, without early retirement.

Table 18 shows the estimates of number of working days lost per year for each disease due to consultations, exams, hospitalizations and convalescence. Length of hospital stay was estimated on the basis of DRGs. It was assumed that convalescence time for AF was equal to length of hospitalization. The employment rate of AF patients (low given the fact that many are past retirement age) was taken into account when calculating mean costs.

Table 18: Indirect costs attributable to atrial fibrillation.

	Consultations		Exams		Hospitalization and convalescence
	Year of diagnosis	**Patients diagnosed in previous years**	**Year of diagnosis**	**Patients diagnosed in previous years**	**Year of diagnosis**
No. of working days lost	2.17	1.66	1.68	1.3	6.5
Cost per patient (€)	52	40	40	31	60
Total annual indirect costs (€)	571335	2876961	436026	2227050	661444
Total (€)			6772816		

The total indirect costs arising from hospitalizations due to AF were calculated by multiplying the indirect costs of days spent in hospital and convalescing by the number of admissions. Adding all these estimates, an overall indirect cost of AF without stroke of €6.77 million was obtained.

Indirect costs of atrial fibrillation with stroke

Estimating the indirect costs of AF with stroke is more complicated, since there are different subgroups of patients depending on the consequences of the stroke and the need for rehabilitation after the event. The findings of the expert panel were used to identify possible scenarios following stroke and the proportion of patients in each scenario, each of which involves different levels of absenteeism resulting from physiotherapy sessions and differences in ability to return to work.

According to the expert panel, 12% of patients who suffer stroke attributable to AF are unable to return to work, 52% need six months of physiotherapy after hospitalization and 22% need 12 months, leading to absenteeism of six and nine months, respectively, assuming that after six months of physiotherapy the patient loses half a working day for each physiotherapy session for the following six months.

The expert panel also calculated that only 0.83% of patients with stroke attributable to AF are unable to work for a period of less than three months. As for those with AF-related stroke AF in previous years, 12% have still not returned to work, while 23% are absent from work for the equivalent of one and a half months a year.

The estimates in Table 19: Indirect costs of stroke attributable to atrial fibrillation. show that the indirect costs of ischemic stroke attributable to AF amount to almost €20 million. Thus, considering all aspects of the indirect costs of ischemic stroke, the total indirect costs attributable to AF are calculated to be €25 million.

Table 19: Indirect costs of stroke attributable to atrial fibrillation.

	Consultations		Exams		Rehabilitation		Hospitalization and convalescence
	Year of diagnosis	Patients diagnosed in previous years	Year of diagnosis	Patients diagnosed in previous years	Year of diagnosis	Patients diagnosed in previous years	Year of diagnosis
No. of working days lost	2.74	1.56	1.17	0.8			22.6
Cost per patient (€)	66	37	28	19			542
Total annual indirect costs (€)	64656	171192	27593	86559	6549699	11352054	153999
Total (€)							18405752

CONCLUSIONS

This analysis showed that 4070 deaths can be attributed to AF in 2010 in Portugal, corresponding to 3.8% of all deaths, and that the total burden of disease attributable to AF is 23084 DALYs. The overall cost of illness is estimated at €140.7 million, around 0.08% of Portugal's gross domestic product. The results are a clear statement of the seriousness of AF in Portugal. Stroke is highly disabling and frequently results in early retirement; as well as the costs involved, the burden of AF reflects the fact that stroke in AF patients is particularly lethal and, for those who survive, disabling. These picture confirms the importance of AF, but at the same time they make it clear that this is an area in which significant health gains can be made

5.2. The relative cost-effectiveness of NOACs in Portugal

BACKGROUND

NOACs are considered to be at least as effective as VKAs, with lower risk of intracranial hemorrhage [79] and with no need for laboratory monitoring of international normalized ratio (INR). Three of these NOACs have been approved to date for reimbursement under the National Health Service (NHS) for AF patients in Portugal: apixaban, dabigatran and rivaroxaban. These three drugs have different mechanisms of action, pharmacokinetics and dosage regimens, and thus offer different therapeutic options for individual patients according to renal dysfunction, age, bleeding risk, history of coronary artery or peripheral arterial disease, and stroke risk.

Although these drugs are more expensive than VKAs, studies on dabigatran and rivaroxaban compared to warfarin for AF patients in Portugal indicate that they are cost-effective in clinical practice.[210,211] Since August 2014, these NOACs have been reimbursed by the NHS for the prevention of thromboembolic events in patients with non-valvular AF. Against this background, it is important for decision-makers to be aware of the health gains and associated costs of the different NOACs. The aim of this study was thus to estimate the cost-effectiveness of NOACs, particularly apixaban (the most recent to have obtained market authorization) compared to warfarin, dabigatran and rivaroxaban.

METHODS

Model structure

A Markov model of cost-effectiveness and cost-utility was used, with a six-week cycle length, the minimum period in which changes in health (or disease) state would be expected, following a cohort of 1000 patients over a lifetime horizon. The model, details of which were recently published by Lip et al.[212], was programmed in Excel using Visual Basic for Applications (Figure 45).

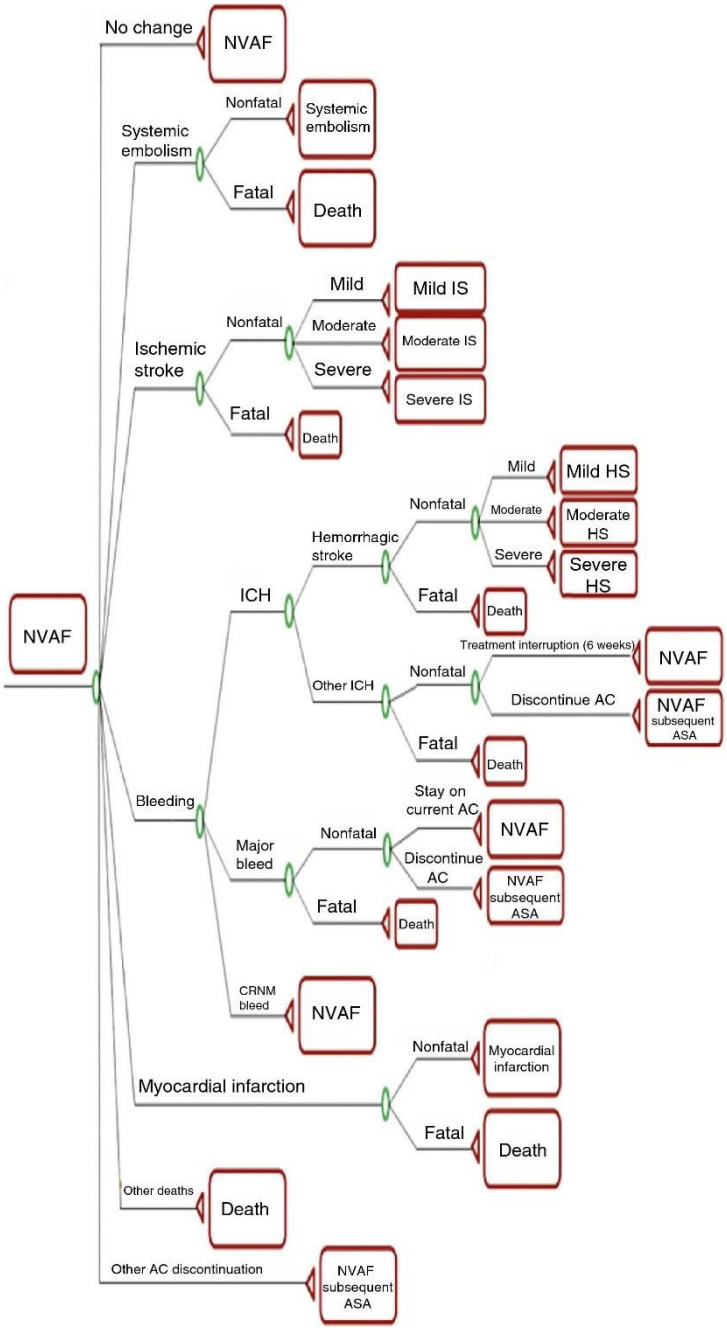

Figure 45: Markov model decision tree. AC: anticoagulants; ASA: aspirin; CRNM: clinically relevant non-major; HS: hemorrhagic stroke; ICH: intracranial hemorrhage; IS: ischemic stroke; NVAF: non-valvular atrial fibrillation; NVAF subsequent ASA: NVAF patients on second-line aspirin. Reproduced from Lip et al Clin Ther 2014.

In the model, the natural history of the disease is represented by 11 mutually exclusive health states: non-valvular AF; mild, moderate or severe non-fatal ischemic stroke; mild, moderate or severe non-fatal hemorrhagic stroke; systemic embolism; myocardial infarction (MI); non-valvular AF with discontinued first-line anticoagulation; and death. After six

weeks the patient can enter, remain in, or transition to another state according to the corresponding transition probability, defined as the likelihood of an event occurring within that period.

The risk of ischemic stroke is calculated according to the patient's $CHADS_2$ score[213] (the method for estimating thromboembolic risk in use at the time of the clinical trials of the drugs under analysis) and the level of anticoagulation for patients treated with warfarin as determined by time in therapeutic range (TTR) of the international normalized ratio (INR). The likelihood of stroke, MI, intracranial bleeding and other major and non-major bleeding increases with age. The model also considers the long-term impact of MI and systemic embolism on mortality, reflected in higher hazard ratios (HR). For patients in the state of non-valvular AF who discontinue first-line anticoagulation, the model structure remains the same but the transition probabilities differ.

Severity of stroke (ischemic or hemorrhagic) is classified according to the modified Rankin scale (mRS)[214]: mild, 0–2; moderate, 3–4; severe, 5; and fatal, 6. All patients with fatal stroke transition to the state of death in the following cycle, while non-fatal stroke is modeled as a tunnel state from which patients can only transition to recurrent stroke or death. Patients can only experience one recurrent stroke in the model, from which the transition is to stroke of the same or greater severity. The model does not allow recurrent MI or systemic embolism, patients either remaining in the same health state or transitioning to death.

At the end of each cycle health care costs, quality-adjusted life years (QALYs) and life years gained are calculated. Levels of health-related quality of life (utilities), clinical outcomes and mortality rates vary according to stroke severity. In accordance with the Portuguese Ministry of Health's guidelines for economic evaluation studies of drugs,[215] published by Infarmed, costs and utilities are discounted at an annual rate of 5%.

Population

In the model's base-case scenario, the characteristics of the population are those of patients enrolled in trials of apixaban, specifically ARISTOTLE,[109] in terms of median age (70 years), gender (64.7% male), and distribution of $CHADS_2$ scores (1–2: 69%; 3–4: 27%; and 5–6: 4%).

Comparators

The results of treatment with apixaban 2.5–5 mg twice daily are compared with (1) dabigatran 150 mg twice daily in patients aged ≤80 years and 110 mg twice daily in patients aged >80 years with high bleeding risk and those treated with verapamil (the dabigatran group) and (2) rivaroxaban 15–20 mg once daily.

Relative effectiveness of the new oral anticoagulants: indirect comparisons

Economic evaluations of new health technologies such as drugs analyze their effectiveness and the associated costs compared to existing options. Assessment of the relative effectiveness of the NOACs is thus one of the central aims of this study. There have to date been no head-to-head studies between the NOACs, so their effectiveness in AF must be estimated by indirect analysis using a common comparator, in this case warfarin.

It is therefore essential to assess the reliability of the estimates of effectiveness used in the model. Therefore, a systematic review of the literature was carried out to identify indirect comparisons between NOACs that provide data on their effectiveness in AF, searching the MEDLINE and Cochrane Library databases in September 2014 using the search terms *meta-analysis*, *indirect comparison, Bayesian, network, apixaban, dabigatran, rivaroxaban and atrial fibrillation*. Ten studies were identified, six frequentist [212], [216-220] and four Bayesian (network meta-analyses).[221-224] The estimates for the various outcomes in these publications are consistent and are similar to those used in the base-case scenario in the economic model.[212] Given the aim of the present study, Lip et al.[212] (frequentist indirect comparison using the method of Bucher et al.[225]) and Mitchell et al.[222] (Bayesian network meta-analysis) probably give the best estimates of the relative effectiveness of the three NOACs in AF, since they use only data from phase III clinical trials and establish associations using HRs, which takes the time factor into account and respects the primary statistical analysis of each trial.

The event rates in the base-case scenario are derived from the HRs reported by Lip et al.[212] (Table 20). Second-line treatment was assumed to be aspirin.

Table 20: Risk estimates of apixaban vs. warfarin and other NOACs. Results are expressed through HR (95%CI)

	Apixaban	Warfarin	Dabigatran 110 mg	Dabigatran 150 mg	Rivaroxaban
Ischemic stroke	1.00	1.09 (0.89–1.35)	1.20 (0.88–1.64)	0.82 (0.60–1.14)	0.98 (0.72–1.33)
ICH[a]	1.00	2.38 (1.72–3.33)	0.73 (0.43–1.26)	1.02 (0.62–1.68)	1.73 (1.08–2.77)
Systemic embolism	1.00	1.00 (0.90–1.10)[b]	1.00 (0.90–1.10)[b]	1.00 (0.90–1.10)[b]	1.00 (0.90–1.10)[b]
Other major bleeding	1.00	1.27 (1.08–1.47)	1.21 (0.97–1.50)	1.37 (1.10–1.71)	1.44 (1.15–1.79)
CRNMB	1.00	1.43 (1.24–1.66)	1.16 (0.99–1.35)	1.30 (1.11–1.53)	1.49 (1.26–1.76)
MI	1.00	1.14 (0.86–1.52)	1.47 (0.96–2.27)	1.46 (0.95–2.24)	0.94 (0.64–1.38)
Other CV hospitalizations	1.00	1.00 (0.90–1.10)[c]	1.00 (0.90–1.10)[c]	1.00 (0.90–1.10)[c]	1.00 (0.90–1.10)[c]

CRNMB: clinically relevant non-major bleeding; CV: cardiovascular; ICH: intracranial hemorrhage; MI: myocardial infarction.

a. Intracranial hemorrhage includes hemorrhagic stroke and other types of intracranial hemorrhage. The proportion of hemorrhagic stroke among intracranial hemorrhage was 77%, 64%, 64%, 41% and 57% for apixaban, warfarin, dabigatran 110 mg, dabigatran 150 mg and rivaroxaban, respectively, according to published studies (secondary analyses of the ARISTOTLE, RE-LY and ROCKET AF trials).

b. Assumed, given the low rate of systemic embolism events in the trials.

c. Assumed to be the same as apixaban.

Source: Lip et al.[212]

Costs

The study adopts the perspective of the NHS and therefore does not analyze indirect costs. Three main types of costs are identified in the model: costs arising from vascular events, costs of anticoagulant therapy, and costs of monitoring and/or routine consultations. Costing is based on (1) Order in Council 20/2014[109] for unit costs of consultations, diagnostic exams and diagnosis-related groups (DRGs); (2) analysis of the database of NHS hospitalizations (DRGs) in 2013[226]; (3) the Portuguese Ministry of Health's drug database (Infomed) for prices of medications, consulted on January 2, 2015[227]; and (4) estimates outpatient care resource use by a geographically representative expert panel of various specialists. For the health states of non-fatal ischemic or hemorrhagic stroke, MI and systemic embolism, costs were divided into acute and long-term maintenance, the acute phase including the first two weeks of hospital stay and the first three months of rehabilitation. The model assumes that the maintenance stage will continue until death and according to the expert panel, includes costs of consultations, emergencies and transport, diagnostic exams, medication and technical assistance. It was not possible to estimate the costs of stroke according to severity (mild, moderate or severe), since there are no data on costs according to the mRS in Portugal. For the other health states only the costs of hospitalization (acute phase) were included.

Overall costs per event, treatment costs and costs of monitoring and routine care are shown in Table 21.

Table 21: Costs arising from vascular events, anticoagulant therapy and monitoring and routine consultations.

Events	Costs (€)	
	Acute (per episode)	Long-term (per month)
Non-fatal ischemic stroke (weighted mean)	8653.26	44.57
Fatal ischemic stroke	6381.20	–
Non-fatal hemorrhagic stroke (weighted mean)	13779.62	41.07
Fatal hemorrhagic stroke	10419.64	
Other intracranial hemorrhage	7932.21	–
GI bleeding	8798.64	–
Non-intracranial and non-GI bleeding	2090.04	–
CRNMB	2514.98	42.32
Systemic embolism	3937.93	–
MI	4560.10	53.61
Other CV hospitalizations	2081.64	–

Source: [b]databases of Centro Hospitalar Lisboa Central and Hospital Fernando da Fonseca; [c]Order in Council 20/2014 [109]; [d]expert panel.

a. Drug prices do not include value-added tax.

CRNMB: clinically relevant non-major bleeding; CV: cardiovascular; GI: gastrointestinal; MI: myocardial infarction.

Mortality

The probabilities of death associated with vascular events in the model are those observed in the trials of the NOACs, with the exception of the fatality rate in MI, which was obtained from Scarborough et al.[228] The model assumes that these probabilities are independent of treatment. For the period corresponding to the duration of the ARISTOTLE trial, mortality from non-vascular causes is assumed to be the same for all three NOACs, and the figures in the ARISTOTLE trial (3.08% for apixaban and 3.34% for warfarin) was used in the model. Mortality after the period analyzed in the clinical trials was estimated on the basis of Portuguese life tables,[229] multiplied by the HRs associated with the population with AF estimated by Friberg et al. to take into account the increased risk of this population.[230] Specifically, the parameters of a Gompertz survival function were calculated by age-group (<75 years and ≥75 years) and by gender. The model includes adjustments to mortality risk to account for the increased mortality associated with AF and different degrees of stroke severity.

Health-related quality of life weights or utilities

The mean values for utilities and disutilities associated with different health states were taken to be the same as those estimated for the UK population by Sullivan et al.[231] There are also disutilities associated with warfarin therapy (unlike the NOACs) and with other vascular events. The model assumes that these disutilities are cumulative. Table 22 summarizes the utilities and disutilities used in the model.

Table 22: Mean utilities and disutilities for the population in the model.

Utility considered in the model for each health state [a]	
AF (baseline utility)	0.7270
Stroke (ischemic and hemorrhagic)	
Mild	0.6151
Moderate	0.5646
Severe	0.5142
Systemic embolism	0.6265
MI	0.6098
Disutilities associated with therapy and with other vascular events (duration)	
Anticoagulants	
Warfarin[b]	0.0130[c]
NOACs	0.0000[c]
Events	
Other ICH (excluding hemorrhagic stroke)	0.1511 (6 weeks)
Other major bleeding (excluding ICH)	0.1511 (14 days)
CRNMB	0.0582 (2 days)
Other CV hospitalizations	0.1276 (6 days)

Source: [a]Sullivan et al.[231]; [b]Gage et al.[232]

c. While under treatment with anticoagulants.

AF: atrial fibrillation; CRNMB: clinically relevant non-major bleeding; CV: cardiovascular; ICH: intracranial hemorrhage; MI: myocardial infarction; NOACs: new oral anticoagulants.

Sensitivity analysis

One-way sensitivity analyses were performed to assess the robustness of the results in terms of the following parameters: (1) use of the HRs estimated by Mitchell et al. (Bayesian network meta-analysis) instead of those estimated by Lip et al.[212]; (2) anticoagulation levels as reported in the clinical trials, instead of those obtained in Portuguese patients; (3) duration of the acute phase of hospitalization taken to be six rather than two weeks; (4)

different costs of stroke depending on severity, with weighting calculated on the basis of UK figures, instead of a uniform cost for stroke of any severity; (5) the same distribution of stroke of similar severity for all NOACs (based on the distribution in the case of apixaban); (6) the same treatment discontinuation rates for non-vascular causes for all comparators as for apixaban (13.2%/year) from the beginning of treatment, instead of the rates reported in the clinical trials; (7) mortality rates after the period covered by the trials taken to be the same as for the general population, thus underestimating mortality; (8) use of different utilities associated with each health state, as estimated in a previous study by Sullivan et al.,[233] and used in other studies of the cost-effectiveness of NOACs[234-236]; and (9) a discount rate for costs and utilities of 0% or 3% instead of 5%.

A probabilistic sensitivity analysis using 2000 Monte Carlo simulations incorporating second-order uncertainty was also performed.[237] The results are presented as the probability of apixaban being cost-effective compared to the other therapeutic options based on a threshold of €20000/QALY, the limit usually taken to be acceptable for funding new health technologies in Portugal.

RESULTS

Event rates and costs

Table 23 shows the number of vascular events associated with each anticoagulant in a cohort of 100000 patients according to the rates derived from the model. The number of vascular events and event-related deaths was lower with apixaban except for hemorrhagic stroke. The difference was greatest for ischemic stroke, other major bleeding, clinically relevant non-major bleeding and event-related deaths.

Table 23: Event rates for each therapeutic option per 100000 patients.

Number of events (total population)	Apixaban	Warfarin	Dabigatran	Rivaroxaban
Ischemic stroke				
Non-fatal	19799	20703	20066	19649
Fatal	2932	2857	3392	3283
Total	22731	23560	23458	22931
Hemorrhagic stroke				
Non-fatal	1602	2040	996	1879
Fatal	1007	2171	702	938
Total	2609	4212	1698	2818
Systemic embolism				
Non-fatal	2138	2175	2403	2263
Fatal	221	225	249	234
Total	2359	2400	2652	2497
Other IC hemorrhage				
Non-fatal	1063	2255	1521	1901
Fatal	159	337	227	284
Total	1221	2591	1748	2185

Other major bleeding				
Non-fatal GI bleeding	5055	5713	7501	8338
Non-fatal non-intracranial and non-GI bleeding	8137	10123	8984	10802
Fatal	269	326	336	391
Total	13461	16159	16822	19530
CRNMB	25248	30700	29914	33367
MI				
Non-fatal	7179	7345	8366	7182
Fatal	1043	1067	1214	1044
Total	8222	8412	9579	8226
Other CV hospitalizations	**116048**	**112390**	**117558**	**116738**
Other reasons for treatment discontinuation	**63406**	**62408**	**72720**	**66616**
Deaths				
Event-related (acute)	5940	7332	6364	6480
Event-related (due to stroke, MI, or systemic embolism)	30524	32066	31694	30779
Other	63536	60602	61942	62741

CRNMB: clinically relevant non-major bleeding; CV: cardiovascular; MI: myocardial infarction; IC: intracranial; GI: gastrointestinal.

Table 24 and Figure 46 present the breakdown of costs associated with the different therapeutic options over a lifetime horizon. Warfarin has the lowest mean cost per patient and rivaroxaban the highest. The total mean cost of apixaban is between these two, with the lowest clinical costs (due to its low vascular event rate) and lowest costs of monitoring and routine care. Although the daily cost of apixaban is lower than dabigatran and rivaroxaban, lifetime costs are greater because the duration of treatment tends to be longer due to its lower discontinuation rate.

Table 24: Total mean cost per patient for each therapeutic option over a lifetime horizon.

Costs (in €)	Warfarin	Apixaban	Dabigatran	Rivaroxaban
Clinical events	5467.29	4989.03	5244.03	5386.30
Therapy	214.42	3754.35	3015.69	3463.96
Monitoring and routine care	3252.29	1254.77	1311.27	1278.31
Total	**8934.16**	**9998.14**	**9570.99**	**10128.56**

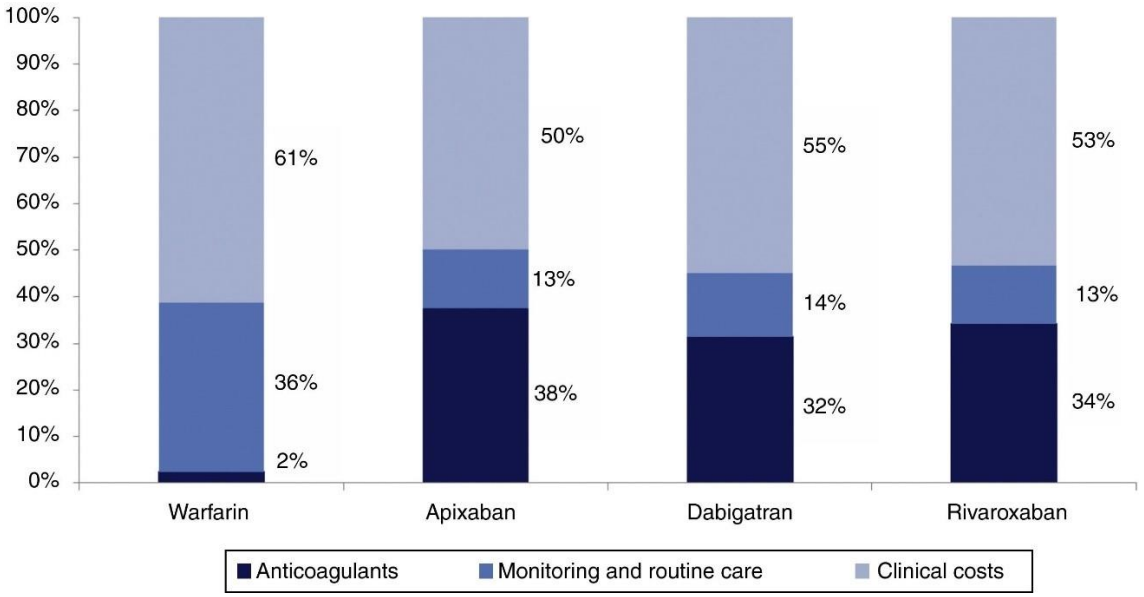

Figure 46: Breakdown of mean total costs per patient for each therapeutic option over a lifetime horizon.

Cost-effectiveness of apixaban compared to the other therapeutic options

Table 25 and Figure 47 show the results of the cost-effectiveness analysis of apixaban compared to the other therapeutic options. As suggested in the literature[238,239] for multiple comparisons, the results are presented as a graph in which the x-axis represents the differences in QALYs and the y-axis the differences in cost between the comparators and the reference therapy (in this case warfarin). The red line linking the points on the graph represents the efficient frontier. The frontier consists of three segments: its slope corresponds to €4367/QALY when it joins the points representing warfarin and dabigatran, €9163/QALY when it joins the points representing dabigatran and apixaban, and is vertical above apixaban because no therapy is more effective. Rivaroxaban is dominated because it is to the left of the cost-effectiveness frontier, presenting greater costs and fewer QALYs than other therapies on the frontier. Rivaroxaban is also dominated by apixaban when analyzed in isolation.

Table 25: Cost-effectiveness analysis of apixaban compared to the other therapeutic options in the base-case scenario.

	Apixaban compared to		
	Warfarin	**Dabigatran**	**Rivaroxaban**
Incremental costs	€1063.98	€427.15	–€130.42
Life years gained	0.19	0.05	0.04
Incremental QALYs	0.19	0.05	0.03
ICER			
Cost per life year gained	€5708.44	€7926.91	Dominant
Cost per QALY gained	€5529.05	€9162.77	Dominant

ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

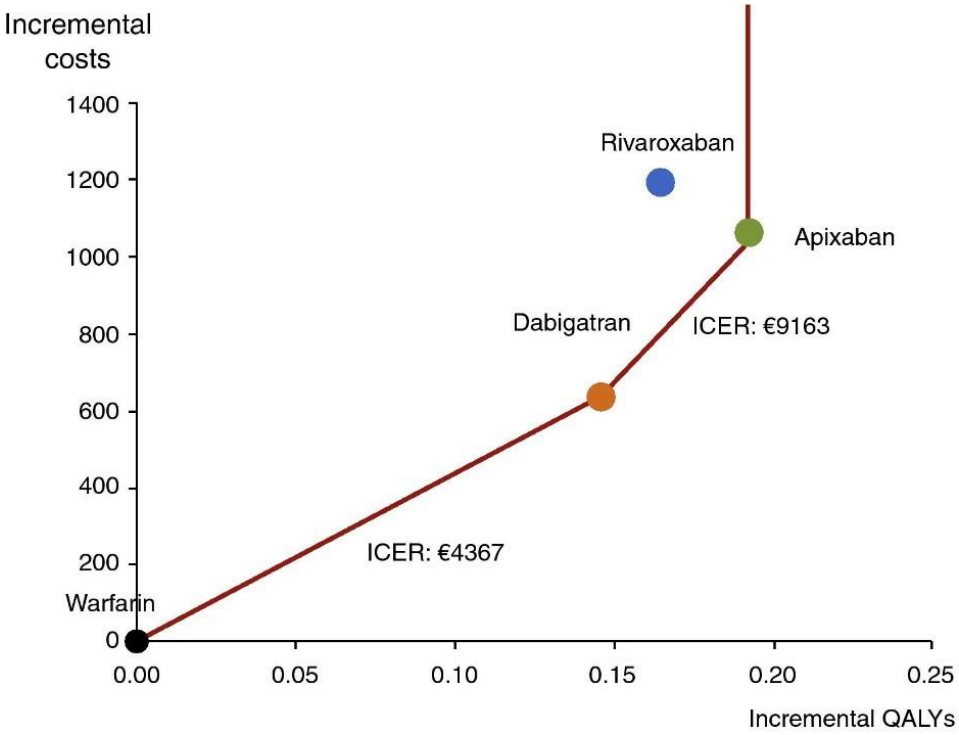

Figure 47: Effectiveness (measured in quality-adjusted life years) and incremental costs of NOACs relative to warfarin (represented by the coordinates 0,0). The red line represents the efficient frontier; the slope of each segment corresponds to the incremental cost-effectiveness ratio between the points defining that segment (ICER).

Sensitivity analysis

The results of the one-way and probabilistic sensitivity analyses confirm the robustness of the study's findings. In the one-way analysis of the nine parameters specified in the Methods section, which reflect a range of alternate scenarios, apixaban is always dominant compared to rivaroxaban. Compared to the other therapeutic options, apixaban presents ICERs well below €20000/QALY, ranging between €4909 and €6741/QALY compared to warfarin and between €5162 and €12016/QALY compared to dabigatran. If it is assumed that discontinuation rates for non-vascular causes remain the same from the beginning of treatment, the costs of apixaban are less than either rivaroxaban or dabigatran. In this case, apixaban is dominant compared to rivaroxaban and, for a threshold of €20000/QALY, is cost-effective compared to warfarin and dabigatran. The results of the sensitivity analyses are summarized in Table 26.

Table 26: Summary of results of sensitivity analyses.

Analysis	Warfarin	Dabigatran	Rivaroxaban
	ICUR (€/QALY)	ICUR (€/QALY)	Net benefit[a] (€)
Use of the HRs estimated by Mitchell et al.[222]	5590.52	10599.93	737.27
Anticoagulation levels as reported in the clinical trials	6740.70	8229.74	874.30
Duration of the acute phase of hospitalization 6 weeks	5531.95	9160.65	730.37
Costs of stroke depending on severity, based on UK figures)	5559.85	8449.95	723.18
The same distribution of stroke of similar severity for all comparators[b]	5601.85	12016.36	564.64
The same treatment discontinuation rates for non-vascular causes for all comparators from the beginning of treatment[b]	5313.84	5161.81	679.93
Mortality rates after the trial period the same as for the general population	5234.19	8444.37	767.13
Utilities estimated by Sullivan et al. [233]	5125.67	7926.91	746.79
Discount rate for costs and utilities of 0% or 3%	5285.03 or 4908.75	8839.03 or 8313.47	720.59 or 1096.69

ICUR: incremental cost-utility ratio.

[a] Based on a willingness to pay of 20 000€/QALY.

[b] Based on the results of the apixaban arm of the ARISTOTLE trial.

In the probabilistic sensitivity analysis, the probability of apixaban being cost-effective for a threshold of €20000/QALY is 96%, 87% and 95% compared to warfarin, dabigatran and rivaroxaban, respectively. If all the comparators are considered together, apixaban is the best alternative from a threshold of €8000/QALY. In this scenario, for a willingness to pay of €20000/QALY, the probability of apixaban being cost-effective is 70% (Figure 48).

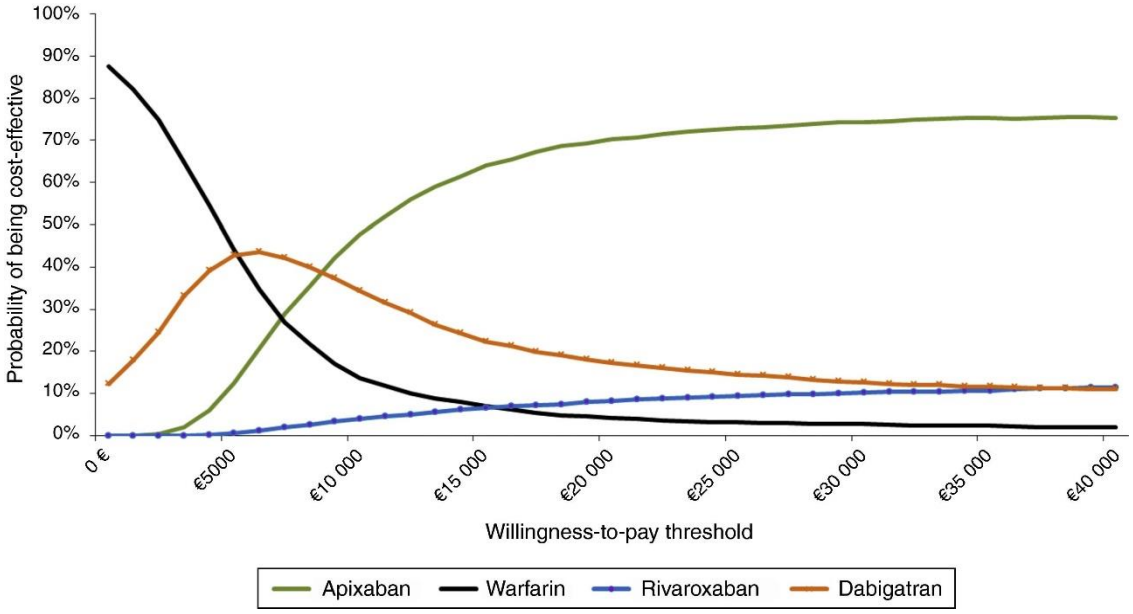

Figure 48: Cost-effectiveness acceptability curves showing the percentage of simulations for each willingness-to-pay value that are cost-effective for each treatment, enabling simultaneous comparison between all the therapeutic options. Apixaban is the best alter alternative from €8000/QALY. For a willingness to pay of €20000/QALY, the probability of apixaban being cost-effective compared to all the other alternatives is 70%.

CONCLUSIONS

The results of the present study show that apixaban is cost-effective compared to warfarin and dabigatran (ICERs of €5529/QALY and €9163/QALY, respectively) and dominant compared to rivaroxaban. The probability of apixaban being cost-effective compared to all the other therapeutic options is 70% for a threshold of €20000/QALY. These conclusions were robust in all the sensitivity analyses performed. This information is useful for healthcare decision-makers when selecting the best option for the individual patient.

5.3. Chapter discussion and conclusions

Considering the previous chapters, one should agree that anticoagulation is increasing due to NOACs, and that no safety problems were observed nor any abnormal pattern of adverse events in the pharmacovigilance. Seems reasonable to assume that NOACs bring health advantages that should be weighed against the limited resources available, taking into account the high price of NOACs and the recent economic restrains.

In order to evaluate the impact of NOACs in the Portuguese society and economy, first the reference condition – AF – was characterized in terms of cost and burden, and then NOACs were evaluated in terms of relative effectiveness, taking VKA as the common comparator.

AF is an important public health issue, because it is the most common sustained arrhythmia in the clinical practice, and it is a risk factor for stroke, a significant cause of morbidity and mortality in Portugal [43]. The risk of stroke is five times higher in patients with AF, increasing with age [32]. Over 15% of strokes are due to AF and they are generally more severe than those not associated with AF [33,35]. Stroke attributable to AF is associated with a 30-day mortality of 25% and one-year mortality of 50% [30]. These patients have longer hospital stays and greater use of health resources [32,33].

According to the FAMA study, the prevalence AF in Portugal was estimated to be 2.5% in the population aged 40 and over, and more than 10% in those aged 80 and over; only 60% of cases were previously diagnosed and acknowledged. As in other countries, the prevalence of AF in Portugal is increasing, probably due to aging populations and better diagnosis. As an example of this trend, there were 4678 admissions with a primary diagnosis of AF in NHS hospitals in Portugal in 2008, while the corresponding figure for 2012 was 6765, an increase of 45%.

The burden of AF in terms of DALYs and costs to society are a clear statement of the seriousness of this condition in Portugal. Stroke is highly disabling and frequently results in early retirement; as well as the costs involved, the burden of AF reflects the fact that stroke in AF patients is particularly lethal and, for those who survive, disabling.

The total burden of disease attributable to AF is 23084 DALYs. The overall cost of illness is estimated at €140.7 million, around 0.08% of Portugal's gross domestic product.

Compared to other diseases/risk factor studied in Portugal, hypercholesterolemia, which is an ominous risk factor (for stroke, coronary artery disease and peripheral artery disease) was

estimated to be related to a loss of 43.773 DALYs while alcoholic beverages consumption retrieved a similar value (41.257 DALYs).[25,34] From all conditions addressed, the tobacco smoking seems to have the greatest burden for society with 145.801 DALYs.[23]

All the referred disease, with exception of AF, are risk factor for multiple diseases. In this analysis, for methodological reasons, the cost and burden of the disease only focused atrial fibrillation and its attributable fraction in stroke. The estimates are very likely to underestimated, because the results do not consider bleeding episodes, including intracranial hemorrhage, a major complication of the anticoagulant therapy. Even though the impact in the society is very important, holding important annual costs (more than €140 million).

Having AF such a significant socio-economic impact in Portugal, it is essential to use the best available resources to address health care in AF patients. Nowadays, considering the known economic restrains, health care resources should be managed thoughtfully, because an increase in the expenses in a certain field will require a decrease in the investment in other areas. Using a cost-effectiveness and cost-utility approach

There were few therapeutic options for this purpose for several decades, when warfarin was the reference treatment, but the development of NOACs has changed the picture. Since the NHS began reimbursing these drugs the number of patients using them has increased significantly, and it is likely that NHS spending on outpatient anticoagulation therapy (currently 4.5%, corresponding to more than €50 million in 2014) will rise further.[240] In the light of this situation, it is important for health decision-makers to have access to estimates of the cost-effectiveness of these NOACs for stroke prevention in AF.

Several cost-effectiveness studies have been published in which a specific NOAC was compared with warfarin. Without exception these studies, carried out in both Europe and the USA, have shown that the NOACs are cost-effective compared to warfarin.[241] However, the results of these studies cannot be used for naive indirect cost-effectiveness comparisons, and they certainly do not reflect the situation in Portugal. An economic evaluation was, therefore, performed based on a previously published model[212] which compared the three NOACs (available in Portugal until the first half of 2016: apixaban, dabigatran and rivaroxaban) to each other, which was adapted for the clinical setting.

The results of the present study show that apixaban is cost-effective compared to warfarin and dabigatran (ICERs of €5529/QALY and €9163/QALY, respectively) and dominant compared to rivaroxaban. The probability of apixaban being cost-effective compared to all the other therapeutic options is 70% for a threshold of €20000/QALY. These results are in agreement

with those of studies in other European contexts, including Belgium,[242] the Netherlands,[234] the UK[212,243] and France,[244] in which apixaban was also cost-effective compared to warfarin and cost-effective or dominant compared to dabigatran and rivaroxaban. The fact that apixaban is the most cost-effective NOAC in these studies may be due to its greater effectiveness, which can be attributed to the lower rate of vascular events associated with its use, particularly ischemic stroke,[212,244,245] major bleeding[222] and event-related deaths.[212,222] A logical consequence is that apixaban presents a lower event-related discontinuation rate and that patients remain under treatment for longer (and thereby benefit in terms of thromboembolic prevention). This lower discontinuation rate explains the higher total lifetime costs of apixaban therapy compared to the other NOACs.

However, other studies have recently been published, in Norway[235] and the UK,[234,236] in which the results are different, with dabigatran being considered cost-effective compared to apixaban (both being superior to rivaroxaban). In these studies, incremental QALYs were 0.2%–1.3% higher with dabigatran than with apixaban, even though the numbers of vascular events used in the analysis were taken from the same clinical trials as those used in the present study.

Various methodological differences may account for these conflicting results: (1) differences in modeling; (2) use of different non-event-related discontinuation rates; (3) modeling of mortality after the trial period; (4) use of different values for the utilities associated with each health state (the present study uses estimates based on Sullivan et al. in 2011,[231] while the other studies were based on the values reported by the same group in 2006[233]); (5) different discount rates.

All of these differences except the first were subjected to one-way sensitivity analysis in the present study that confirmed the robustness of the main results. Therefore, the differences between the studies cannot be explained by these parameters. They may thus be due to differences in modeling, including the ways in which the states of the Markov model are specified, different cycle lengths, the use of a single level of severity for stroke, and differences in cost estimates (which are influenced by the resources and characteristics of health care systems and the prices of drugs in each country). A quantitative analysis of these questions is beyond the scope of this study.

Some studies have suggested that the cost-effectiveness of the NOACs depends on the level of anticoagulation control, in that they will tend to be more cost-effective when anticoagulation control is poor. In particular, it has been suggested that dabigatran is less cost-effective in well-controlled patients.[71,246] However, the results of sensitivity analysis for this parameter showed no significant differences

Limitations

In the study of cost and burden of AF, for methodological reasons, the results presented in this study underestimate the cost and burden of the disease. They do not consider bleeding episodes, including intracranial hemorrhage, a major complication of the anticoagulant therapy used as prophylaxis against stroke in AF patients. Heart failure associated to atrial fibrillation (e.g. tachymyopathy) was not accounted for the overall outpatients' expenses, and loss of productivity. It is important to stress that the burden and cost shown could be lower because it is estimated that 40% of the patients are treated with oral anticoagulants.

The cost-effectiveness study had limitations in terms of the data used, particularly for the number of events, since these were taken from clinical trials with short follow-up periods (2–3 years), which may not reflect the actual effectiveness of each drug. Furthermore, in the absence of head-to-head comparisons between the NOACs, cost-effectiveness was estimated indirectly, using warfarin as a common comparator, and so it was not possible to control for differences in baseline patient characteristics, trial design, anticoagulation level or risk profile determined by $CHADS_2$ score (although the results on the cost-effectiveness of apixaban are similar in the subpopulation with higher $CHADS_2$ scores).[247] According to the literature review carried out by the authors of the present study, the estimates of effectiveness used in this study are consistent with those in published indirect comparisons and the results did not change when other estimates obtained by Bayesian methods were used.[222]

In all studies of this chapter the consumption of resources in the outpatient care was estimated by a panel of experts from different regions and different specialties that handle with AF patients.

In order to assess the robustness of the results obtained, a comprehensive sensitivity analysis for several factors was performed. The results are reassuring because qualitatively the results did not change, i.e. all NOACs remained in the cost-effectiveness quadrant, apixaban was cost-effective compared to warfarin and dabigatran, and dominant compared to rivaroxaban.

CONCLUSIONS

NOACs shown to be cost-effective compared with VKA for the prevention of thromboembolic events in atrial fibrillation. In this model the apixaban showed to be cost-effective compared to warfarin (ICER € 5529/ QALY) and dabigatran (ICER € 9163/ QALY), and dominant compared to rivaroxaban. This study considered an acceptability threshold for the payment of € 20000/QALY, and the likelihood of apixaban be cost-effective compared to the other options was 70%. Thus the NOACs may bring benefits in terms of health outcomes and resource utilization in a significant condition such as AF which leads yearly to the loss of 23,084 DALYs and has expenses of 141 million € (57% in direct costs and 43% in indirect costs).

Chapter VI

Overall discussion and conclusions

Part of the contents of this chapter were published or are related to the following articles:

- Caldeira D, Ferreira JJ, Pinto FJ, Costa J. Safety of non-vitamin K antagonista oral anticoagulants - coronary risks. ***Expert Opin Drug Saf.*** 2016;15:731-40.

- Caldeira D, Costa J, Ferreira JJ. Bridging Anticoagulation in Patients with Atrial Fibrillation. ***N Engl J Med.*** 2016;374:91-2.

- Caldeira D, Costa J, Ferreira JJ, Lip GY, Pinto FJ. Non-vitamin K antagonist oral anticoagulants in the cardioversion of patients with atrial fibrillation: systematic review and meta-analysis. ***Clin Res Cardiol.*** 2015;104:582-90.

- Caldeira D, Costa J, Ferreira JJ, Pinto FJ. Thromboembolic risk in the initiation, switch and interruption/re-initiation of oral anticoagulants: do newcomers improve outcomes? Insights from a meta-analysis of RCTs. ***Int J Cardiol.*** 2014;177:117-9.

6.1. Discussion

AF is an important public health issue, particularly in Portugal, since it is a risk factor for stroke, a significant cause of morbidity and mortality in this country [43].

About a third of Portuguese patients with AF are not aware of their condition. As AF can remain silent until complications occur[55,56], clinical screening is indicated for individuals aged 65 and over[57]. The main complications of AF are thromboembolic events, particularly stroke, which is among the most important causes of death and disability. Therefore, it is without surprise that AF holds an important impact, as shown in the cost of illness and burden of disease study. It was estimated that in 2013 AF was responsible for a cost of €140 million (about 0.08% of Portuguese gross domestic product) and 23084 DALYs [248]. Most of these DALYs and costs are related to stroke. The risk of stroke is five times higher in patients with AF, increasing with age[32]. Over 15% of strokes are due to AF and they are generally more severe than those not associated with AF [33,35]. Stroke attributable to AF is associated with a 30-day mortality of 25% and one-year mortality of 50% [30]. These patients have longer hospital stays and greater use of health resources [32,33].

It is well known that anticoagulation with VKA, such as warfarin, significantly decreases the risk of stroke and systemic embolism in these patients[35]. Nevertheless, according to the results presented in this dissertation[78,192], the reported prevalence of anticoagulation in Portuguese AF patients is very low (40%) and the degree of anticoagulation control with VKA in those that are anticoagulated is suboptimal[78,192]. Thus, despite the evidence and the recommendations supporting the use of oral anticoagulants in AF patients, a significant proportion of the population at risk is not adequately anticoagulated. This scenario definitely contributes to the high AF associated mortality and morbidity. According to the estimates presented in this dissertation, the burden of disease attributable to AF in Portugal is about 23084 disability-adjusted life years (DALYs). Therefore, there is still room for improvement and both prescription of oral anticoagulants and increased control of oral anticoagulation among AF patients is likely to have an important healthcare impact.

NOACs have been proven to be at least as efficacious as other alternative treatment options, in particular VKA, with a more favorable pharmacological profile. As shown the use of NOACs is rising continuously. As known, individual RCTs are designed for efficacy outcomes and this condition hinders their ability to evaluate safety[49]. The systematic reviews with meta-

analysis of phase III RCTs, in the absence of specific antidotes, support that NOACs (apixaban, dabigatran, edoxaban, rivaroxaban) are associated to a significantly decreased risk of major bleeding and fatal bleeding events compared to VKA. Intracranial hemorrhage risk is also lower, however the incidence of major GI, intraocular and pericardial bleeding events is comparable to VKA. Possible concerns about severe liver and renal adverse events, as well as insomnia risk and immunity issues (and infection risk) associated to NOACs are not supported by the data presented in this dissertation. The overall tolerability profile (serious adverse events) was more favorable with NOACs in comparison to VKA. Acceptability results (discontinuation risk) were heterogeneous, but the overall drug-related discontinuation risk was lower with NOACs in comparison to VKA.

In Portugal, three of these NOACs have been reimbursed and widely available, following the published cost-effectiveness studies[210,211], including the cost-effectiveness study presented in this dissertation[182]. NOACs are cost-effective interventions for the Portuguese reality. Therefore, taken into consideration the efficacy, safety, convenience and cost-effectiveness of NOACs, as well as the high incidence and prevalence of the target clinical indications (in particular AF), the rise of oral anticoagulants due to an increase of NOACs prescription is is expected as it follows a rational drug prescription. Following steps in the improvement of the use of oral anticoagulants/NOACs are related to specific prothrombotic indications or circumstances, to the optimal management of major bleeding events, including the use the new specific antidotes adequately, and keeping pharmacovigilance on track. It is critical to stress that the pharmacologic similarities of NOACs and VKA are minimal and that rules for VKA discontinuation should not be immediately extrapolated for NOACs[249]. In the other hand, the anticoagulant properties of NOACs are likely to be as effective as standard peri-cardioversion anticoagulation in the prevention of peri-procedural period[250].

6.1.1. Implications for research and clinical practice

Research

The results retrieved in this thesis showed that the proportion of patients previously anticoagulated was low and that the number of oral anticoagulants prescribed is increasing overtime. It remains unknown whether this prescription pattern owes mostly to the new diagnosed cases or to a change in the physicians' attitude regarding patients with prothrombotic conditions, namely AF. A contemporary cross-sectional study of the prevalence of oral anticoagulation in AF patients in Portugal is mandatory in order to assess these data.

It is important to mention that prescription data does not consider other important elements of successful drug therapy delivery: the compliance and persistence [251]. In this field, antithrombotic drugs are critical as most of the studies show a low rate of persistence (<50%) including studies with NOACs[252,253], which strongly suggests that this area should be improved.

The use of antithrombotic drugs in prothrombotic conditions requires regular clinical supervision. Nowadays, is clear that in almost situations, the use of anticoagulants is recommended in diseases such as AF, despite the increased risk of bleeding with these drugs. Therefore, the critical question that requires to be research is which oral anticoagulant provides a better net clinical benefit[174]. This outcome is defined heterogeneously, as it results from different perceptions in how different outcomes should be combined. Despite all it seems extremely important to standardize the definition in order to proceed homogeneously with investigations, as previously recalled[174].

Despite the safety data presented in this dissertation, other potential safety issues such as the risk of myocardial infarction associated to NOACs should be addressed in the near future as uncertainty exists concerning some NOACs[254-256]. Trials are ongoing specifically designed to address NOACs safety in AF patients with coronary artery disease undergoing coronary stenting (RE-DUAL PCI NCT02164864; NCT02415400; NCT02334254). Rather than overviewing NOACs safety regarding myocardial infarction risk, they also aim to evaluate which may be the best combination of antithrombotic drugs in these patients [256].

Another important remark concerns the observational studies ("real world data") of patients treated with oral anticoagulants, particularly NOACs. These studies may be

hierarchically inferior to RCTs but have advantages concerning the absence of restrains in patients' selection and well as the period of exposure to drugs which may be longer that RCTs and help to uncover potential long term adverse events. These studies are essential to ascertain the transferability of both efficacy and safety of trials towards effectiveness and population safety. National registries as occurs with acute coronary syndromes (NCT01642329) should be encouraged.

Clinical practice

The results presented show that NOACs have a good safety profile regarding bleeding and non-bleeding adverse events. Regarding bleeding events, in the absence of specific antidotes NOACs decreased the risk of major bleeding events (including fatal events). These results emphasize the safety of NOACs and that physician fears regarding the bleeding with these novel agents are not supported. Antidotes specific for NOACs are under development with promising results, in order to further improve healthcare and outcomes in bleeding patients[21-25].

With efficacy at least as similar to VKA and a good safety profile, the rise in the prescription of oral anticoagulants with NOACs, is likely to decrease the burden of AF in Portugal. There are still three important gaps in the care of these patients. The first is the development of a national guideline for atrial fibrillation, and second is the establishment of oral anticoagulant use as marker of healthcare quality in primary care setting and the third was the allowance of NOACs triplicate medical prescription to maintain long-term treatment.

6.2. Final remarks

The proportion of patients treated with oral anticoagulants is increasing due to NOACs. These drugs overcame warfarin in term of prescriptions, improving a marker of quality in the management of some prothrombotic conditions such as AF, which was very low in Portugal where about 40% patients with AF were anticoagulated. NOACs also warrant a predictable anticoagulant effect without multiple drug-drug and drug-food interactions. The potential impact of this characteristic is inversely proportional to the degree of anticoagulation control with VKA, which was found to be low (TTR 61%). Therefore, NOACs may play an important role in the improvement of healthcare management of AF. This is particularly important because AF holds an important burden for society, and has important costs associated (0.08% of the GDP).

Massive NOACs prescription, does not seem encompass any safety risks. The best available evidence from phase III RCTs supports that NOACs (apixaban, dabigatran, edoxaban, rivaroxaban) are associated to a significant decreased risk of major bleeding and fatal bleeding events compared to VKA. Intracranial hemorrhage risk is also decreased, however the incidence of major GI, intraocular and pericardial bleeding events is comparable to VKA. The other findings did not support the possible concerns about severe liver and renal adverse events, as well as insomnia risk and immunity issues (and infection risk) associated to NOACs. The overall tolerability profile (serious adverse events) was more favorable with NOACs in comparison to VKA. Acceptability results (discontinuation risk) were however heterogeneous, although the overall drug-related discontinuation risk was lower with NOACs in comparison to VKA.

The number of spontaneously reported adverse events related to oral anticoagulants is increasing in Portugal. The number of ADRs weighted by the number of prescription has reached its peak in 2012 and has been decreasing since then. Although the majority of reports and ADRs were related to NOACs. One quarter of the reported NOACs ADRs were hemorrhagic and 10% were related to thromboembolic events (lack of efficacy), probably reflecting the unexpectedness of these events taking into account the results of the clinical trials.

In the Portuguese scenario, all NOACs were cost-effective compared with VKA.

In my opinion, NOACs are valuable therapeutic options under the right indications (such as non-valvular AF) and the data generated by the research projects presented in this dissertation support that the healthcare in the oral anticoagulation field has changed significantly towards an era where NOACs prevail.

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Appendix

List of Grants and Prizes.

Grant by the Fundação para a Ciência e Tecnologia (FCT) with the Interno-Doutorando scholarship SFRH/SINTD/96409/2013.

Prize for best poster on "Health technology assessment in cardiovascular disease", promoted by CUTEheart, and hosted by the Portuguese Congress of Cardiology 2016 (2016) with "Risk of major gastrointestinal bleeding with non-vitamin K antagonist oral anticoagulants: systematic review and meta-analysis"

Authors: Daniel Caldeira, Márcio Barra, Adriana Ferreira, Ana Augusto, Andreia Rocha, João Costa, Fausto J. Pinto, Joaquim Ferreira.

List of full publications.

As first author

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ARTIGO DE REVISÃO

Prevalência da anticoagulação oral em doentes com fibrilhação auricular em Portugal: revisão sistemática e meta-análise de estudos observacionais

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PALAVRAS-CHAVE
Fibrilhação auricular;
Anticoagulação;
Prevalência;
Coumarinicos;
Varfarina;
Antagonistas da vitamina K

Resumo
Introdução e objetivo: A anticoagulação oral é uma terapêutica eficaz na prevenção de eventos tromboembólicos, em doentes com fibrilhação auricular (FA). A presente revisão pretendeu estimar a prevalência da terapêutica anticoagulante oral em doentes com FA em Portugal.
Métodos: Foi realizada uma pesquisa nas bases de dados MEDLINE, Índex de Revistas Médicas Portuguesas e Catálogo Bibliográfico do Sistema Integrado de Bibliotecas da antiga Universidade Clássica de Lisboa (SIBUL). Estudos observacionais nacionais que reportavam a proporção de doentes anticoagulados com fibrilhação auricular foram incluídos. A estimativa combinada de prevalência de doentes com FA anticoagulados e o respetivo intervalo de confiança 95% (IC95%) foi determinada com recurso a meta-análise.
Resultados: Dos sete estudos incluídos, três estudos foram realizados em ambiente hospitalar e quatro foram realizados na comunidade em geral. Do total de 891 doentes com FA, a estimativa de prevalência de doentes anticoagulados foi de 40% (IC95% 32-48%).
Conclusões: A prevalência de doentes com FA anticoagulados na população estudada é baixa. É necessário promover a mudança dos hábitos de prescrição de anticoagulantes em doentes com FA em Portugal, em concordância com as recomendações internacionais.

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KEYWORDS
Atrial fibrillation;
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Warfarin;
Vitamin K antagonists

The prevalence of oral anticoagulation in patients with atrial fibrillation in Portugal: Systematic review and meta-analysis of observational studies

Abstract
Introduction and Objectives: Oral anticoagulation (OAC) is an effective treatment in the prevention of thromboembolic events in patients with atrial fibrillation (AF). The aim of this review was to estimate the prevalence of OAC therapy in patients with AF in Portugal.
Methods: MEDLINE, the Index of Portuguese Medical Journals and SIBUL (the Bibliographic Catalog of the Integrated Library System of the University of Lisbon) were searched for Portuguese observational studies reporting the proportion of anticoagulated patients with AF. The pooled estimated prevalence of anticoagulated patients and respective 95% confidence interval (CI) were determined by means of a meta-analysis.
Results: Seven studies were included for analysis, of which four were conducted in a hospital environment and three in the general community. These studies enrolled a total of 891 patients with AF. The pooled estimated prevalence of anticoagulated patients was 40% (95% CI: 32–48%).
Conclusions: The prevalence of OAC in Portuguese AF patients is low. There is a need to promote change in OAC prescribing habits for AF patients in Portugal, in accordance with international guidelines.

Introdução

A fibrilhação auricular (FA) é a arritmia mais prevalente na prática clínica, com uma prevalência estimada para a população portuguesa com mais de 40 anos de 2,5% (estudo FAMA), a qual aumenta com a idade, atingindo 6,6% na 8.ª década de vida e 10,4% em indivíduos com 80 ou mais anos de idade[1].

No estudo FAMA, cerca de um terço dos doentes com FA desconhecia o diagnóstico. Por se tratar de uma patologia que pode permanecer silenciosa até ao aparecimento de uma complicação[2,3], o seu rastreio clínico está indicado em doentes a partir dos 65 anos[4]. As principais complicações da FA são os eventos tromboembólicos, nomeadamente o acidente vascular cerebral (AVC). Para a prevenção destes eventos, está recomendada a terapêutica com anticoagulantes orais em doentes com fatores de risco tromboembólico[4].

No presente estudo pretendemos estimar a prevalência da terapêutica com anticoagulantes orais em doentes portugueses com FA, através de uma revisão sistemática e meta-análise de estudos epidemiológicos.

Métodos

Critérios de elegibilidade

Foram considerados elegíveis estudos observacionais conduzidos em Portugal Continental e/ou arquipélagos que incluíssem doentes com FA ou *flutter* auricular (independentemente do tipo: paroxística, persistente ou permanente) e que reportassem a proporção dos doentes que estavam anticoagulados. Estudos que incidiram sob populações específicas ou doentes referenciados para intervenções específicas (p. ex. terapêutica ablativa da FA) foram excluídos, porque a inclusão destes estudos introduziria um viés ao não ser representativo da população geral de doentes com FA.

Bases de dados e pesquisa

Foram pesquisas as bases de dados eletrónicas MEDLINE, Índex de Revistas Médicas Portuguesas e Catálogo Bibliográfico do Sistema Integrado de Bibliotecas da antiga Universidade Clássica de Lisboa (SIBUL), entre 2005 e outubro de 2013. A pesquisa incluiu ainda a revisão da listagem de referências dos estudos incluídos e das revisões da literatura encontradas. Não foram incluídos resumos de *posters* ou comunicações orais apresentados em congressos.

Seleção dos estudos e extração dos dados

Os estudos potencialmente elegíveis foram selecionados de forma independente por dois autores, com base nos critérios de inclusão e exclusão referidos. Os dados foram extraídos de forma independente para uma folha sistemática de recolha de dados que incluía as características demográficas dos estudos, os determinantes tromboembólicos das populações e a proporção de doentes anticoagulados.

Os estudos incluídos foram avaliados de forma qualitativa, utilizando critérios relacionados com amostragem/representatividade, avaliação e análise de resultados[5]. Nenhum estudo foi excluído com base na avaliação do risco de viés dos estudos.

As discordâncias foram resolvidas por consenso entre os autores.

Síntese dos dados

Foi utilizado o *software* Stata® *Statistical Software Package*, Versão 11.0 (StataCorp LP, College Station, Texas, EUA) para agregar os resultados através de meta-análise e determinar a estimativa global de prevalência de doentes com FA anticoagulados. Nos estudos que estratificavam o risco tromboembólico da população, o denominador da prevalência foi a proporção de doentes com indicação para anticoagulação. Os resultados dos estudos individuais e agregados foram expressos em proporções (prevalência) e intervalos de confiança de 95% (IC95%). Para a agregação dos dados dos estudos foi utilizado o método de ponderação pelo inverso da variância dos resultados de cada estudo. Dada a expectativa de existência de heterogeneidade significativa entre os estudos foi utilizado por defeito o modelo de efeitos aleatórios de DerSimonian e Laird[6].

A heterogeneidade estatística foi avaliada e quantificada através de teste I^2. O I^2 é uma medida da percentagem da variação global entre os resultados dos estudos que é atribuível à heterogeneidade[7]. Um teste I^2 superior ou igual a 50% determina heterogeneidade significativa[8].

As estimativas da prevalência foram calculadas separadamente em função do local/contexto do estudo epidemiológico: comunidade e hospitalar.

Resultados

Foram incluídos para análise sete estudos[1,9–14]. A Figura *Online* 1 mostra o fluxograma da seleção dos mesmos. Três estudos eram transversais[1,9,13] e quatro apresentavam um desenho longitudinal (três coortes retrospetivos[10–12] e um estudo coorte prospetivo[15]). Três estudos foram realizados na comunidade[1,9,13] e quatro a nível hospitalar[10–12,14]. Os sete estudos incluíram um total de 891 doentes com FA considerados potencialmente elegíveis para serem medicados com anticoagulação oral. A amostra de indivíduos com FA dos estudos variou entre 21-261 doentes, na sua grande maioria idosos, uma vez que a idade média variou entre 77-85,5 anos (o que classifica de uma forma global como uma população com risco tromboembólico elevado). Três dos estudos incluíram doentes com doença valvular significativa ou prótese valvular mecânica: um deles incluiu 29% de doentes com patologia valvular pelo menos moderada ou prótese valvular[12]; Ascenção incluiu 20% de doentes com estenose mitral[9]; Dores incluiu 6% de doentes com FA de etiologia valvular[11]. As ferramentas utilizadas para a estratificação do risco tromboembólico foram o $CHADS_2$, CHA_2DS_2-VASc e modelo proposto pelas *guidelines* conjuntas do *American College of Cardiology/America Heart Association/ European Society of Cardiology 2006* (Tabela 1). Dois estudos não reportaram o uso de qualquer ferramenta[1,10].

As principais características dos estudos incluídos estão mencionadas na Tabela 1. A qualidade metodológica dos estudos incluídos foi razoável. O principal fator de risco de viés metodológico foi a falta de representatividade da amostra de alguns estudos, pela sua avaliação exclusiva em ambiente hospitalar ou pela análise de subgrupos de doentes. A avaliação qualitativa está presente na Figura *Online* 2.

De acordo com os resultados da meta-análise destes sete estudos, a prevalência da terapêutica anticoagulante oral em doentes portugueses com FA é de 40% (IC = 95%: 32-48%), sendo a prevalência superior nos estudos realizados a nível da comunidade (45%; IC95%: 37-52%) do que a nível hospitalar (36%; IC95%: 24-48%) Esta diferença não teve, no entanto, significado estatístico (p = 0,20). Os resultados estão presentes na Figura 1.

Para avaliar o impacto da inclusão de estudos com diferentes ferramentas de estratificação do risco tromboembólico (por exemplo (CHADS2, CHA2DS2-VASc) avaliámos os resultados dos diferentes subgrupos. As diferenças entre as estimativas obtidas pelos diferentes métodos não foram significativas (p = 0,31). A prevalência de doentes anticoagulados foi superior (44% [37-51%] *versus* 30% [15-45%]) nos estudos que reportaram o uso destas ferramentas comparativamente com aqueles que não as utilizaram, sem contudo atingir significado estatístico (p = 0,10).

Discussão

A FA é tema relevante em termos de saúde pública, particularmente em Portugal, dado que constituiu um fator de risco para a ocorrência de AVC, uma importante causa de morbilidade e mortalidade[15]. O risco de AVC é cerca de cinco vezes superior em doentes com FA, aumentando com a idade[16]. Mais de 15% dos AVC devem-se à manifestação da FA e são, em média, mais graves do que aqueles que não estão associados à FA[17,18]. Os AVC atribuíveis à FA estão associados a uma taxa de mortalidade de 25% a 30 dias e de 50% a um ano[17]. Nos doentes com AVC, pelo mau prognóstico que condiciona, a FA está associada a um aumento do tempo de internamento e consumo de recursos de saúde[19,20].

Existe evidência sólida de que a anticoagulação oral reduz o risco dos eventos tromboembólicos. Os antagonistas da vitamina K estão associados a uma redução significativa de 64% do risco relativo de AVC[21] e os novos anticoagulantes orais (inibidores diretos da trombina e Xa) mostraram ser pelo menos tão eficazes quanto os antagonistas da vitamina K.

A baixa prevalência de doentes anticoagulados encontrada nesta revisão enfatiza a necessidade de mudança dos hábitos de prescrição. Esta proporção aproxima-se daquela encontrada no estudo italiano ISAF, em que a prevalência de anticoagulação oral foi de 46%[22]. Contudo, outros dados da mesma área geográfica, baseados em unidades cardiológicas, mostram um aumento significativo na proporção de doentes anticoagulados com indicação para esta terapêutica[23]. No entanto, outros estudos recentes mostram uma perspetiva mais otimista. O registo internacional prospetivo GARFIELD reporta uma prevalência de 67% de anticoagulação oral nos doentes com FA e CHADS-VASc ≥ 2[24]. O registo alemão ATRIUM, baseado em dados dos cuidados de saúde primários, encontrou uma prevalência de anticoagulação de 75% de doentes com FA e risco tromboembólico elevado[25], e o registo PREFER *in* AF, baseado em dados de sete países europeus, mostrou uma elevada utilização de anticoagulantes nesta população: 85%[26].

Tanto em contexto de ensaios clínicos como em mundo real, diversos são os motivos invocados pelos clínicos para não anticoagular doentes com FA[24,27].

Tabela 1 Principais características dos estudos incluídos

Estudo	Desenho do estudo Local	Período do estudo	Amostra (n)	Idade média/mediana (anos)	Indicação para anticoagulação
Ascenção[9]	Estudo transversal Comunidade (Rede de Médicos Sentinela)	Junho 2003 - novembro 2003	243	84% > 65 anos	$CHADS_2 \geq 2$, estenose mitral ou trombo intracavitário
Reis et al.[10]	Estudo retrospetivo Hospital (HFF)	Janeiro 1996 - dezembro 2004 (utilizados dados de 2004)	108	78,6	-
Bonhorst et al.[1]	Estudo transversal Comunidade	-	119 (diagnóstico prévio de FA)/69% FA total	77	-
Dores et al.[11]	Estudo retrospetivo hospitalar (HSFX)	Outubro 2006 - outubro 2007	126	77	Doente com risco moderado ou elevado de acordo com *Guidelines* ACC/AHA/ESC 2006
Jorge et al.[12]	Estudo retrospetivo hospitalar (HUC)	Dezembro 2005 - junho 2007	161	80,9	$CHADS_2 \geq 2$
Sá et al.[13]	Estudo transversal Comunidade (USF Saúde em Família – Maia)	2011	31	85,5	CHA_2DS_2-VASc ≥ 2
Pereira-Da-Silva et al.[14]	Estudo prospetivo Hospitalar (CHLC)	Abril 2011 - outubro 2011	103	79,6	CHA_2DS_2-VASc ≥ 2

ACC/AHA/ESC: *American College of Cardiology/America Heart Association/ European Society of Cardiology*; CHLC: Centro Hospitalar Lisboa Central; FA: fibrilhação auricular; HFF: Hospital Prof. Dr. Fenando Fonseca; HSFX: Hospital São Francisco Xavier; HUC: Hospitais da Universidade de Coimbra; USF: Unidade de Saúde Familiar.

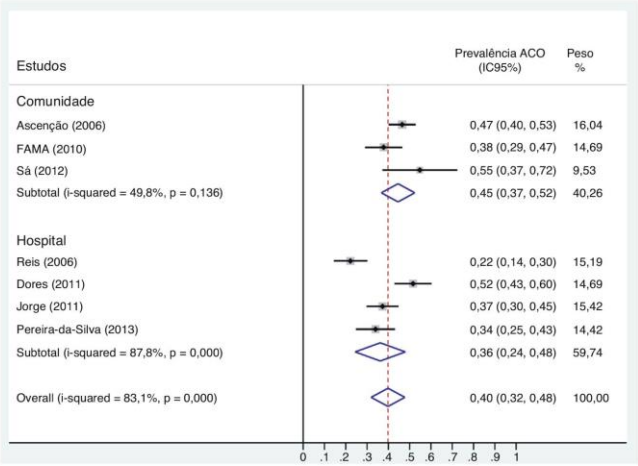

Figura 1 Prevalência da anticoagulação oral em doentes com FA. ACO: anticoagulação oral.

Num estudo hospitalar, Dores avaliou em 19% a proporção de doentes não-anticoagulados com o diagnóstico de FA[11]. Os principais motivos invocados para esta atitude foram o risco/discrasia hemorrágica, história de alcoolismo, doença renal e impossibilidade do controlo do INR[11].

Pereira-da-Silva avaliou os preditores de não prescrição de anticoagulantes orais em 103 doentes candidatos e os motivos subjacentes[14]. Após análise multivariável, o estado acamado/síndrome demencial e o elevado número de fatores de risco hemorrágicos foram preditores de não prescrição. Dos doentes não anticoagulados (68 doentes), os motivos mais prevalentes para a não prescrição da terapêutica anticoagulantes foram: risco hemorrágico elevado (56%), considerar ser pequeno o benefício (22%), incapacidade de seguir o esquema terapêutico (10%) e dificuldade na monitorização do INR (7%)[14].

Em relação aos anticoagulantes orais da nova geração, os motivos da sua não-prescrição baseiam-se no custo elevado, no facto de alguns destes fármacos não serem comparticipados, no pequeno benefício esperado e no risco hemorrágico[14].

Apesar do seu custo, os novos anticoagulantes, para além de se apresentarem como opções custo-efectivas[28,29], permitem ultrapassar algumas barreiras à prescrição, nomeadamente pela ausência de monitorização regular do INR, por terem potencialmente menos interações medicamentosas e alimentares.

As atuais normas de orientação da Sociedade Europeia de Cardiologia recomendam uma estratificação do risco tromboembólico utlizando o CHA_2DS_2-VASc para determinar quem não beneficia de anticoagulação oral (CHA_2DS_2-VASc = 0)[4,30]. Alguns estudos desta revisão utilizaram a ferramenta previamente recomendada para estratificação do risco tromboembólico, o $CHADS_2$[31], ou o algoritmo proposto pelas *guidelines* conjuntas do *American College of Cardiology/America Heart Association/ European Society of Cardiology 2006*[32]. Dado que estas ferramentas subestimam/excluem uma fração de doentes que poderia beneficiar de anticoagulação, a prevalência de anticoagulação nos doentes com indicação poderia ser ainda menor de acordo com o CHA_2DS_2-VASc.

Para além dos pontos já mencionados, dois estudos incluíram uma proporção considerável de doentes com patologia valvular significativa ou próteses valvulares[9,12]. A probabilidade de estes doentes não estarem anticoagulados é menor do que a de um doente com FA não-valvular, no entanto, em ambos os estudos a prevalência da anticoagulação oral é baixa.

A elevada heterogeneidade encontrada não é rara em estudos de prevalência, para ela contribuindo múltiplos fatores inerentes aos doentes, instituições e prescritores, que diferem entre os vários estudos.

A diferença de heterogeneidade entre os estudos realizados na comunidade em comparação com os realizados em meio hospitalar pode ser devida a diversos fatores. O mais evidente é a inclusão do estudo de Reis[10] (o mais antigo dos estudos hospitalares, 2006) na meta-análise. Este estudo caracterizou a terapêutica anticoagulante nos internamentos do ano de 2004. No total, ocorreram 122 internamentos por FA em 2004. Destes 122 doentes, 108 tiveram indicação para fazer anticoagulação a longo prazo. Dos doentes com indicação apenas 22,2% tiveram alta anticoagulados[10].

A reduzida taxa de anticoagulação observada nos estudos hospitalares, particularmente no estudo referido previamente, pode ter várias explicações. A idade e a presença de comorbilidades podem contribuir para uma perceção do risco hemorrágico aumentado. A coexistência de ambas razões tem sido referida como um entrave à prescrição de anticoagulantes por parte dos médicos, por receio de hemorragias graves ou por acreditarem num risco embólico menor comparativamente com o risco hemorrágico[33]. Adicionalmente, alguns estudos foram realizados numa época prévia à publicação do estudo *Birmingham Atrial Fibrillation Treatment of the Aged Study* (*BAFTA*), que mostrou superioridade da varfarina (INR alvo 2,0-3,0) em relação ao ácido acetilsalicílico na prevenção de eventos cardiovasculares em doentes com 75 anos ou mais, sem diferenças significativas no risco hemorrágico[34].

Limitações

As conclusões desta revisão devem ser avaliadas de acordo com as limitações inerentes à metodologia usada (meta-análise utilizando dados globais dos estudo e não dados dos doentes individuais). A inclusão de populações com diferentes amostras, idades, locais de avaliação (comunidade *versus* hospital) e metodologia utilizada para adequar a terapêutica ao risco tromboembólico ($CHADS_2$, CHA_2DS_2-VASc) deve ser considerada (heterogeneidade clínica), para além da heterogeneidade estatística já esperada.

Conclusões

A prevalência de anticoagulação oral em doentes portugueses com FA é de cerca de 40%. Apesar da evidência e recomendações existentes em relação ao benefício desta terapêutica na redução do risco tromboembólico nos doentes com FA, uma proporção muito significativa da população em risco não está medicada. A anticoagulação oral nestes doentes pode ser entendida como um índice de qualidade dos cuidados de saúde que urge alterar.

Anexo. Material adicional

Pode consultar material adicional a este artigo na sua versão eletrónica disponível em doi:10.1016/j.repc.2014.02.014.

Conflito de interesses

Os autores declaram não haver conflito de interesses.

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RESEARCH ARTICLE Open Access

Evaluation of time in therapeutic range in anticoagulated patients: a single-center, retrospective, observational study

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Abstract

Background: The percentage of time during which the patients have the INR within the target values (i.e. Time in Therapeutic Range [TTR]) is a measure of anticoagulation quality with Vitamin K Antagonists (VKA). To evaluate the quality of anticoagulation using TTR according to the Rosendaal method, we performed an observational, retrospective study. We included all outpatients who attended the cardiology anticoagulation clinic of a Portuguese hospital (2011–2013), whose target INR was 2.0-3.0.

Results: 377 VKA-treated patients were evaluated. Of these, 72.4% had non-valvular atrial fibrillation. Patients were followed for a mean period of 471 days. The mean TTR was 60.3% (SD 19.3%) and 44.3% of the patients had a mean TTR < 60%. Patients were at high risk of bleeding (INR > 4.5) and at high thrombotic risk (INR < 1.5) during, respectively, 1.7% and 4.7% of the time.

Conclusions: Anticoagulation control needs to be improved. These results are informative for all stakeholders: patients, health care professionals, and policymakers.

Keywords: Anticoagulation quality, TTR, Warfarin, Vitamin K antagonist

Background

Vitamin K Antagonists (VKA) such as warfarin, acenocoumarol and phenpromcom are widely prescribed oral anticoagulant drugs. The main indications are atrial fibrillation (AF), valvular prosthesis, venous thromboembolism and intracavitary thrombus. These drugs' efficacy and safety depends on International Normalized Ratio (INR) monitoring. The absence of standard dosages of VKA turns imperative to perform serial INR tests and make dosages adjustments when the results are out of the range.

INR levels above and under pretended values are associated to increased risk of hemorrhagic and thromboembolic events, respectively [1,2].

Time in therapeutic range (TTR) is a measure of quality of anticoagulation and lower values are related to adverse events [3].

TTR knowledge is important to identify the current standard of anticoagulation care and establish new goals. Additionally TTR is an important input to determine the cost-effectiveness of new oral anticoagulants [4].

The most comprehensive published data about TTR in Portuguese patients comes from RE-LY study. This trial included Portuguese patients and mean TTR was 61% [5,6].

TTR data retrieved from randomized controlled trials may overestimate those from real world [7]. Therefore we aimed to retrospectively review the charts of patients from a single-center anticoagulation consultation in order to estimate TTR.

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Methods

Study design and setting

We conducted a retrospective cohort study of patients treated with vitamin K antagonists followed in Cardiology Anticoagulation Clinic a Portuguese single-centre from January 2011 to July 2013, in order to determine the TTR of the centre. We obtained Institutional Board and Ethics Committee approval for this study.

Participants, variables and statistical analysis

We identified all patients treated with vitamin K antagonists followed in the Outpatient Cardiology Anticoagulation Clinic. Patients' data were retrieved from a database which contains the all INR records obtained in the visits. All patients were submitted to nurse led INR checking using CoaguCheck® XS system and follow-up was made according to INR value, and hospital protocol or physicians preferences.

For analysis, we included patients whose target INR was between 2.0 and 3.0 (patients with INR targets between 2.5 to 3.5, including patients with mechanical heart valves were excluded). To better characterize the quality of long-term anticoagulation all patients under 2 months of follow-up tests or <6 INR tests were excluded [8]. We have characterized the demographic and clinical characteristics of the population. For each patient we evaluated all available INR values to calculate the individual TTR according to the Rosendaal method [9]. This method uses linear interpolation to assign an INR value to each day between successive observed INR values.

Patients were clustered into subgroups according to the reason/indication for anticoagulation: non-valvular AF; valvular AF (patients with mitral stenosis, severe aortic stenosis, severe mitral regurgitation, biologic prosthetic valves, valve repair); venous thromboembolic disease; and others (including left ventricular dysfunction, intracavitary thrombus, non-compaction cardiomyopathy).

The primary outcome was the TTR, a continuous outcome. Secondary outcomes were: 1) TTR < 60%, a marker of poor quality in the control of INR [3,10]; 2) time under therapeutic range (INR < 2.0); 3) time over therapeutic range (INR > 3.0); 4) time with increased thrombotic risk (INR < 1.5); 5) time with increased hemorrhagic risk (INR > 4.5).

All analyses were conducted using SPSS software version 9.1. Statistical summary measures such as arithmetic mean and median were used to characterize the population. Standard deviation (SD) and interquartile range were used to evaluate data dispersion. Multivariate logistic regression analysis was performed to identify risk factors for TTR < 60%, at a significance level of 0.05. Chi-square test was performed for the comparison of dichotomic data across groups. One-way ANOVA was used to evaluate differences between TTR across indications (more than 2 groups). The results were considered to be statistically significant at a p-value <0.05.

Ethics

Hospital Garcia de Orta Institutional Board and Ethics Committee have approved this project.

Results

We found 501 patients treated with VKA with target INRs between 2.0 and 3.0, with their INR recorded in the database between January 2011 and July 2013. About 377 patients had the minimum required follow-up/number of tests to meet the inclusion criteria.

The mean age was 71 years, and 59.4% of the patients were male. Most of the patients had non-valvular AF (72.4%), while valvular AF (19.1%) and venous thromboembolic disease (3.4%) were less common. The population's average CHA_2DS_2-VASc was 3.58.

Patients were followed for a mean period of 471 days, having performed on average 17 INR tests per year each patient. The average time between two tests was 25.4 days.

Table 1 shows the main characteristic of the population.

The mean TTR was 60.3% (SD 19.3%) and the median 63% (interquartile range 47.9-74.8%). About 44.3% of the patients evaluated have a mean TTR < 60%, and are at increased risk of thrombotic and hemorrhagic events.

The female gender was the only characteristic that was significantly associated to poor anticoagulation control

Table 1 Main characteristic of included patients

Characteristics	Population (N = 377)
Age – years	
Mean (SD)	71.0 (10.4)
Median (IQR)	72.0 (66–79)
Female sex – no. (%)	153 (40.6)
Previous stroke or transient ischemic attack – no. (%)	56 (14.9)
Heart failure – no. (%)	160 (42.4)
Diabetes mellitus – no. (%)	101 (26.8)
Hypertension - no. (%)	253 (67.1)
Vascular Disease History – no. (%)	122 (32.4)
Indication for anticoagulation	
Non-valvular AF	273 (72.4)
Valvular AF*	72 (19.1)
Venous thromboembolism	13 (3.4)
Others	19 (5.1)
CHA_2DS_2-VASc	
Mean (SD)	3.58 (1.62)
Median (IQR)	3 (2–5)

*Mitral stenosis, severe aortic stenosis, severe mitral regurgitation, biologic prosthetic valves, valve repair. AF: Atrial Fibrillation; IQR: Interquartile Range; SD: Standard Deviation

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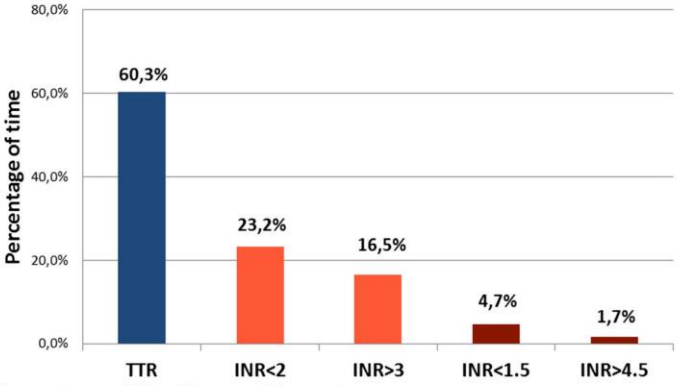

Figure 1 Time in therapeutic range (TTR) and time out of therapeutic range.

(TTR < 60%) in the multivariable regression analysis with an odds ratio 1.73 and 95% confidence interval 1.14-2.62 (p = 0.01).

The average percentage of time that patients remained above (INR > 3.0) and below the target INR (INR < 2.0) was 16.5% and 23.2%, respectively. Patients were at high risk of bleeding (INR > 4.5) 1.7% of the time, and at high thrombotic risk (INR < 1.5) 4.7% of the follow-up period. Figures 1 and 2 illustrate these results.

Non-valvular AF was the most prevalent indication for anticoagulation. The mean CHA_2DS_2-VASc was 3.65 (SD 1.58). In this cluster of patients, the average TTR was 59.3% (SD 19.8%) and the median was 61.8% (interquartile range 47.4-73.7%). These patients were on average 23.4% of the time below therapeutic range (INR < 2.0), and 17.3% of the time over INR 3.0. The mean percentage of time with high thrombotic risk (INR < 1.5) was 5.3%, and 1.7% of the time patients were at high risk of bleeding.

There were no significant differences in average TTR between the different indications for VKA treatment (p = 0.18). The proportion of patients with low anticoagulation control also was not different across conditions (p = 0.53). Table 2 shows the mean TTR and the proportion of TTR < 60% according to the main indication for anticoagulation.

Discussion

VKA have been shown to be effective in the treatment and prevention of thromboembolic events, however they possess many drug-drug and drug-food interactions, as well as a narrow therapeutic window. Despite high number of studies in the field, much of the individual variability in response to warfarin therapy remains unexplained and, therefore careful monitoring is required in order to reduce the risk of tromboembolic events and bleeding complications. This process is costly and inconvenient for many patients [11]. The quantification of TTR allows characterization and of anticoagulation control quality.

According to our study, the TTR of this population of anticoagulated Portuguese patients was 60.3% during a mean follow-up of 1.3 years. Forty-four percent of this population had a TTR < 60%. This means that an important proportion of patients are at increased risk of major adverse events [3,10,12].

The results show an inadequate control of anticoagulation from a global point of view [13,14]. Additionally, the identification of the female gender as a predictor of low TTR goes in line with the recent SAMe-TT_2R_2 that identifies women (Sex – female; S in the acronym) as

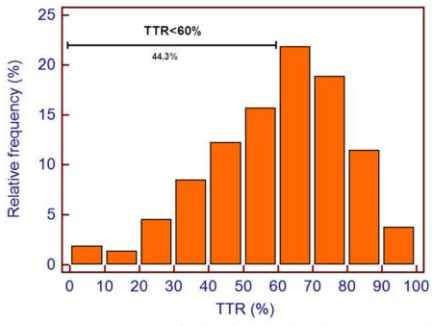

Figure 2 Histogram with relative frequencies of TTR values and proportion of patients with TTR < 60%.

Table 2 Mean Time in Therapeutic Range (TTR) according to main indication for anticoagulation

Population	Mean TTR (SD)	TTR < 60% (%)	Patients	Average follow-up (years)
Non-valvular AF	59.3% (19.7%)	128 (46.7%)	274	1.27
Valvular AF	64.0% (18.6%)	29 (40.3%)	72	1.44
Venous thromboembolism	54.6% (24.4%)	5 (38.5%)	13	1.18

AF: Atrial Fibrillation; SD: Standard Deviation; TTR: Time In Therapeutic Range.

population at risk for inadequate anticoagulation with VKA [15].

Recent large trials with new oral anticoagulants in AF provided further data about world-wide quality of anticoagulation control. In ROCKET-AF the mean TTR was 55.2% (63% in Western Europe, 64% in North America) [16], and the median TTR was 66% in ARISTOTLE [17]. The RE-LY study had a median TTR of 67.2% and presented TTR data according to countries, including Portugal. The benchmark countries were Sweden, Finland, and Australia with TTR values of 77% (Sweden) and 74% (Finland and Australia) [6]. The results obtained in our study are similar to those of the RE-LY study for Portugal (61%), and are overall in accordance to those reported in the literature [7,18].

In our study we calculated individual patient TTR using a longitudinal linear extrapolation of INR values through a method proposed by Rosendaal as it is more time sensitive than other methods (takes into account the number of days within the range) [19].

The experience of other national centres about the quality of anticoagulation control reports data of INR tests within pretended ranges, rather than longitudinal TTR method. In an anticoagulation clinic 1067 INR controls were performed in two months in 687 patients. About 71% of the tests were within the range [20]. Another single centre experience of INR telemonitoring showed that 83% of the tests were within the range [21].

Applying our data to those retrieved from randomized controlled trial, in centres with TTR of 61%, new oral anticoagulants tend to be safer and/or more effective than VKA. In RE-LY, all dosages (110 mg and 150 mg bid) had a significant lower risk of intracranial bleeding, with a similar risk major bleeding, while in the prevention of thromboembolic events only the dosage of 150 mg showed a significant risk reduction compared to warfarin. The efficacy of rivaroxaban was not statistically different from warfarin but there was a trend towards rivaroxaban in the prevention of thromboembolic complications (HR 0.70; IC95% 0.48-1.03). Apixaban was safer in terms of major bleeding with an efficacy likely to be better than warfarin (HR 0.73; IC95% 0.53-1.00).

Limitations

The main limitation of this study was that it was a retrospective, non-randomised cohort of patients anticoagulated with VKA followed in the Cardiology Anticoagulation Consultation of a single-center. However this is still, to the best of our knowledge, the first study evaluating the quality of anticoagulation in Portugal with Rosendaal TTR.

Patients with non-valvular AF with stable therapeutic INR values are usually proposed for discharge to primary care follow-up. The data here presented does not account for INR values registered in other facilities, such as in the emergency room or during hospitalizations. These reasons may limit the conclusions of this study.

We did not focus on other patients with very high thrombotic risk such as those carrying mechanical heart valves (because INR target is 2.5-3.5). So the data here presented cannot be extrapolated to such subgroups.

We used CHA_2DS_2-VASc score all patients, nevertheless we recognize that the use of such tool in valvular AF or in VTE may not be adequate. This score identifies prevalent risk factors for thromboembolism and we used to describe the population without performing any analysis on this basis.

Conclusions

The average TTR of this center was 60.3%. An important proportion of patients was at high risk of events (TTR < 60%). At our center, anticoagulation control should be improved. When out of therapeutic range, patients were more commonly prone to prothrombotic risk due to the higher percentage of time with INR < 2.0. These results are informative for all stakeholders: patients, health care professionals, and policymakers.

Abbreviations

AF: Atrial fibrillation; INR: International normalized ratio; TTR: Time in therapeutic range; VKA: Vitamin K antagonists.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DC contributed to the concept and design, data acquisition, data analysis, and interpretation of the data; wrote the first draft of the manuscript; critically revised the manuscript; and gave final approval of the submitted manuscript. IC contributed to the data analysis, and interpretation of the data; wrote the first draft of the manuscript; critically revised the manuscript; and gave final approval of the submitted manuscript. BS, GM, CG, CM, IJ, and HP contributed significantly to interpretation of data, critically revised the manuscript, and gave final approval of the submitted manuscript.

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Healthcare delivery, economics and global health

ORIGINAL ARTICLE

Non-vitamin K antagonist oral anticoagulants and major bleeding-related fatality in patients with atrial fibrillation and venous thromboembolism: a systematic review and meta-analysis

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ABSTRACT

Objective Non-vitamin K antagonist oral anticoagulants (NOACs) are efficacious and safe antithrombotic drugs but the non-availability of an antidote for potential fatal haemorrhagic events is clinically perceived as a strong limitation. We aimed at evaluating the risk of haemorrhage-related fatalities associated with NOACs in patients requiring long-term anticoagulation.

Methods MEDLINE, Cochrane Library and Web of Science databases were searched in November 2014 for atrial fibrillation (AF) or venous thromboembolism (VTE) phase III randomised controlled trials (RCT) comparing NOACs with vitamin K antagonists (VKAs) or low molecular weight heparin (LMWH) followed by VKAs. Pooled OR and 95% CIs were estimated through meta-analysis. Heterogeneity was assessed with the I^2 test.

Results Eleven studies were included: 5 on AF and 6 on VTE. A total of 100 324 patients were evaluated in 4 rivaroxaban, 3 dabigatran, 2 apixaban and 2 edoxaban studies. NOAC-treated patients had a 47% odds reduction compared with VKA (OR 0.53; 95% CI 0.42 to 0.68; I^2=0%; 3 events avoided per 1000 patients) and 64% odds reduction compared with LMWH–VKA (OR 0.36; 95% CI 0.15 to 0.84; I^2=0%; 1 event avoided per 1000 patients) regarding fatal bleeding risk. Case fatality due to major bleeding was lower in NOAC-treated patients both in AF (OR 0.68; 95% CI 0.48 to 0.96; I^2=37%; 1 death avoided per 39 major bleedings) and VTE (OR 0.54; 95% CI 0.22 to 1.32; I^2=0%) patients. AF survivors of major bleeding events treated with NOACs had lower mortality compared with patients treated with VKAs (OR 0.57; 95% CI 0.45 to 0.73; I^2=0%; 78 events avoided per 1000 survivors to major bleeding).

Conclusions These data suggest that NOACs decrease the risk of fatality cases related to major bleeding events, particularly in AF patients. These results support the safety profile of NOACs even without having a widely available drug-specific antidote.

INTRODUCTION

Non-vitamin K antagonist oral anticoagulants (NOACs) have granted market authorisation for the prevention of thromboembolic events in patients at high thrombotic risk. There is strong evidence supporting the fact that the efficacy of NOACs compares at least similarly with other drugs considered the standard of care in these conditions.[1–3] The safety profile also exceeds other antithrombotic drugs, namely vitamin K antagonists (VKAs), in the predictability of the dose–response relation, lack of coagulation monitoring and dose adjustment needs, fast onset of action[3] and decreased risk of intracranial haemorrhage.[4]

However, the absence of an antidote for NOACs for emergent haemorrhagic events is considered by many as one of the main drawbacks of this group of drugs and argues against their routine use.[5–7]

Our objective was to evaluate the risk of haemorrhage-related fatalities associated with NOACs in comparison with VKAs or sequential treatment with low molecular weight heparin (LMWH) and VKAs. We reviewed the fatality cases, directly or indirectly related to the major bleeding events, reported in randomised controlled trials (RCTs) of patients requiring long-term anticoagulation.

METHODS

This systematic review followed PRISMA guidelines.[8] Reporting of statistical data followed SAMPL guidelines.[9]

Eligibility criteria

All phase III RCTs comparing NOACs, including inhibitors of IIa (dabigatran) or Xa (apixaban, darexaban, edoxaban, or rivaroxaban), against VKAs or sequential treatment of LMWH and VKAs in patients with atrial fibrillation (AF) or venous thromboembolism (VTE) were included.[4 10] We selected these conditions due to the requirement for medium-term and long-term anticoagulation. Patients with recent hip or knee arthroplasty were excluded because these would only require short-term anticoagulation and the inclusion of such trials would increase bias associated to statistical effects of rare events. Studies comparing NOACs with antiplatelet drugs were also excluded.

Fatal bleeding events are not frequent. Therefore, we considered only phase III RCTs to avoid bias in risk estimation due to statistical effects of small-size underpowered studies on meta-analysis results.[11–14] Furthermore, we were interested in determining the risk associated with

commonly used doses of NOACs, which are typically used in phase III RCTs.

All published RCTs were considered for inclusion irrespective of background therapy, NOAC treatment duration or follow-up. Only trials reporting fatal and non-fatal bleeding events were included.

Our primary objective was to evaluate overall mortality directly or indirectly associated with major bleeding events. Therefore, our main outcomes were incidence of fatal bleeding, major bleeding case fatality rate and all-cause mortality in major bleeding survivors.

Fatal bleeding events were defined as events in which the cause of death was a direct consequence of a major bleeding event. Major bleeding case fatality rate was defined as the ratio between fatal bleeding and major bleeding events. In patients who survived a major bleeding event we also evaluated the all-cause mortality.

Whenever possible, we used the International Society of Thrombosis and Haemostasis (ISTH) definition for major bleeding: fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome and/or bleeding causing a fall in haemoglobin level of 2 g/dL or more, or leading to transfusion of two or more units of whole blood or red cells.[15] We were not restrictive and other definitions were allowed when ISTH major bleeding outcome was not available.

Information sources and search method

Records of potentially eligible studies were identified through an electronic search of bibliographic databases from inception to November 2014 (MEDLINE, CENTRAL at Cochrane Library and Web of Science). Search strategy details are provided in the online supplementary data. No language restrictions were applied. We screened and cross-checked identified systematic reviews and meta-analyses evaluating NOACs, as well as reference lists of reports of potential eligible studies.

Study selection and data collection process

Titles and abstract of records obtained in the search process were screened by two investigators. Doubts and disagreements were solved by consensus. Whenever needed, a third element was consulted. Selected studies were assessed in full text to determine its appropriateness for inclusion. Data from included studies were independently extracted by three authors to an electronic form. Retrieved data items were study design, year of publication, patients' characteristics and drugs used, outcomes of studies, data of required outcomes and estimates adjustments. Data were double-checked for software entry before analyses by an additional author.

Should the studies present different estimates of the outcomes of interest, estimates reporting the most precise or adjusted measures of association were used. Otherwise, we used crude OR or derived it from raw data.

Quality of reporting was independently analysed by two authors using the Cochrane Collaboration Risk of Bias Tool to assess risk bias and to evaluate reporting.[16] Arbitrarily, we classified the overall risk of bias as low (if ≥80% of all analysed items in all included studies had a low bias risk), moderate (if this percentage ranged between 50% and 80%) and high (if this percentage was below 50%). Doubts or disagreements were solved through consensus or a third element. Risk-of-bias graphs were derived from this tool.

Data analysis

We used RevMan V.5.3.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) for statistical analysis and to derive forest plot showing the results of individual studies and pooled analysis.

Outcomes data were summarised as dichotomous data. We compared NOACs with VKAs (with or without an initial period using concomitantly LMWH) through random effects meta-analysis weighted by the inverse-variance method to estimate pooled OR and 95% CIs. The effect measurement estimate chosen was OR because relative estimates are more similar across studies with different designs, populations and lengths of follow-up than absolute effects.[17]

Heterogeneity measured as the percentage of total variation between studies due to heterogeneity was assessed through the χ^2 and I^2 tests.[18] We used a random effects model independently of the existence ($I^2 \geq 50\%$, $P_{heterogeneity} < 0.05$ in χ^2 test) or absence of substantial heterogeneity between the results of studies because we pooled results of studies with different designs and patients' characteristics. When significant differences were found we determined the number of events avoided per 1000 treated patients with NOACs, using as baseline risk the event rate reported in the control group (VKAs or LWMH–VKAs). For case fatality of major bleeding, in case of significant differences, the absolute risk measure reported was the number needed to treat, that is, the number of patients needed to experience a major bleeding event with NOACs required to avoid one bleeding fatality compared with VKAs.

Results were stratified according to indication for anticoagulation (AF or VTE) to explore differences in outcome estimates. Differences between subgroups were evaluated through random effects model due to the lower risk of false-positive results.[19]

In order to minimise the risk of type I errors, trial sequential analyses (TSA) were performed using TSA V.0.9 β (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark, 2011). TSA evaluated whether cumulative data were adequately powered to evaluate the outcomes.[20] The required information size (and the O'Brien-Fleming adjacent trial sequential α spending monitoring boundaries) was calculated based on a two-sided 5% risk of a type I error, 20% risk of a type II error (power of 80%), risk reduction based on the pooled analysis and the incidence of events in the control group. Results were considered adequately powered if significance is reached with either minimum sample size or crossing trial sequential α spending monitoring boundary.

Publication bias was assessed through visual inspection of funnel plots asymmetry and Egger's and Peters' regression tests.[21 22] The latter evaluates the linearity of effect estimate with sample size.

RESULTS

After reviewing all potentially eligible reports for appropriateness for inclusion, 11 studies[23–30 S1–S3] were included: 5 studies on AF[23 25 26 29 S2] and 6 studies on VTE.[24 27 28 30 S1 S3]

A flowchart of study selection phases is depicted in online supplementary figure S1.

All included studies were international multicentre double-blinded RCTs with the exception of one Japanese study[29] and three open-label studies.[23 27 28] Three post hoc analyses of RCTs were also included as these provided the required data.[S4–S6] RE-LY additional major bleeding events were considered for analysis.[S7] Characteristics of included studies are summarised in table 1.

Table 1 Characteristics of included studies

Year	Study acronym	Mean/ median age	Active group	Control group	Follow-up	Primary outcome
Atrial fibrillation						
2011	ARISTOTLE	70	9088 patients Apixaban 5 mg BID	9081 patients dose adjusted Warfarin	1.8 years	Stroke or systemic embolism
2009	RE-LY	71	6015 patients Dabigatran 110 mg BID; 6076 patients Dabigatran 150 mg BID	6022 patients Warfarin OD Target INR 2.0–3.0	2 years	Stroke or systemic embolism
2009	ENGAGE-AF	72	7035 patients Edoxaban 60 mg OD; 7034 patients Edoxaban 30 mg OD	7036 patients Warfarin OD Target INR 2.0–3.0	2.8 years	Stroke or systemic embolism
2011	ROCKET-AF	73	7131 patients Rivaroxaban 20 mg OD	7133 patients Warfarin OD Target INR 2.0–3.0	1.9 years	Stroke or systemic embolism
2011	J-ROCKET	71	639 patients Rivaroxaban 15 mg OD	639 patients Warfarin ODTarget INR 2.0–3.0; except >70 years INR 1.6–2.6	>1 year	Stroke or systemic embolism
Venous thromboembolism						
2013	Hokusai-VTE	56	4118 patients Edoxaban 60 mg OD or 30 mg OD if CrCl 30–50 mL/min or <60 kg	4122 patients Warfarin OD Target INR 2.0–3.0	8.2 months	Recurrent symptomatic VTE
2010	EINSTEIN Acute DVT	56	1731 patients Rivaroxaban 15 mg BID for 3 weeks and 20 mg OD afterwards	1718 patients Enoxaparin and VKA OD Target INR 2.0–3.0	According to intended treatment duration: 3 months (12%), 6 months (63%) and 1 year (25%)	Recurrent VTE events
2009	RE-COVER	55	1273 patients Dabigatran 150 mg BID	1266 patients Warfarin OD Target INR 2.0–3.0	30 days	VTE events and thromboembolic-related death
2013	RE-MEDY	55	1430 patients Dabigatran 150 mg BID	1426 patients Warfarin OD Target INR 2.0–3.0	6 months	VTE or VTE-related death associated with VTE
2012	EINSTEIN–PE	58	2420 patients Rivaroxaban given 15 mg BID for 3 weeks, followed by 20 mg OD	2413 patients enoxaparin and VKA Target INR 2.0–3.0	According to intended treatment duration: 3 months (5%), 6 months (57%) and 1 year (38%)	Symptomatic recurrent VTE
2013	AMPLIFY	57	2691 patients Apixaban 10 mg BID for 7 days, and then 5 mg BID for 6 months	2704 patients with subcutaneous enoxaparin, followed by VKA	6 months	VTE events or VTE-related death

AF, atrial fibrillation; BID, twice daily; DVT, deep vein thrombosis; INR, international normalised ratio; OD, once daily; VKA, vitamin K antagonist; VTE, venous thromboembolism.

A total of 100 324 patients were included (72.73% with AF) with a mean age of 71 years for AF patients and 56 years for VTE patients. Mean follow-up period ranged from 1 to 2.8 years for AF trials, and most of VTE patients had 6 months follow-up. RE-COVER[24] was the only trial having 30 days of follow-up.

Among all included patients, 56.5% were treated with NOACs: 11 799 patients treated with apixaban (2 RCTs), 14 794 patients treated with dabigatran (3 RCTs), 18 187 patients treated with edoxaban (2 RCTs) and 11 921 patients treated with rivaroxaban (4 RCTs). A total of 302 fatal bleeding events among 4291 major bleeding events were reported in these RCTs.

Overall, the risk of bias of included studies was low to moderate (78% of the bias items were rated as having a low bias risk, as depicted in online supplementary figure S2). Although three studies had an open-label design, we considered it appropriate to include these trials because lack of blinding is not associated with over or sub-estimates of objective outcomes in clinical trials, in particular mortality.[58] Despite the availability of adjusted estimates for postbleeding mortality in RE-LY[23] and ARISTOTLE,[25] none of the other studies provided adjusted estimates for fatal bleeding or case fatality rate of major bleeding. Therefore, we considered all trials to be at high risk of bias regarding this characteristic (last column in the online supplementary figure S2).

Fatal bleeding

The 11 RCTs included reported data on fatal bleeding. In AF patients, NOACs were associated with a 47% odds reduction in the risk of fatal bleeding (OR 0.53, 95% CI 0.42 to 0.68; $I^2=0\%$, $\chi^2=3.85$, $P_{heterogeneity}=0.43$). The number of fatal bleeding events avoided per 1000 patients treated with NOACs was 3 (95% CI 2.7 to 3.5) in a period of 1–2.8 years.

TSA showed that cumulative evidence is adequately powered (sample size >24 760 patients) and that statistical significance was reached after the third published trial with a cumulative sample size over the minimum required (see online supplementary figure S3).

In VTE patients, NOACs were also associated with a significant 64% odds reduction in the risk of fatal bleeding (OR 0.36; 95% CI 0.15 to 0.84; $I^2=0\%$, $\chi^2=1.91$, $P_{heterogeneity}=0.86$). Despite not reaching the minimum required sample size (79.0% of the required information size), TSA showed that sufficient evidence was established to show a risk reduction with NOACs regarding fatal bleeding, with crossing of the upper boundary of

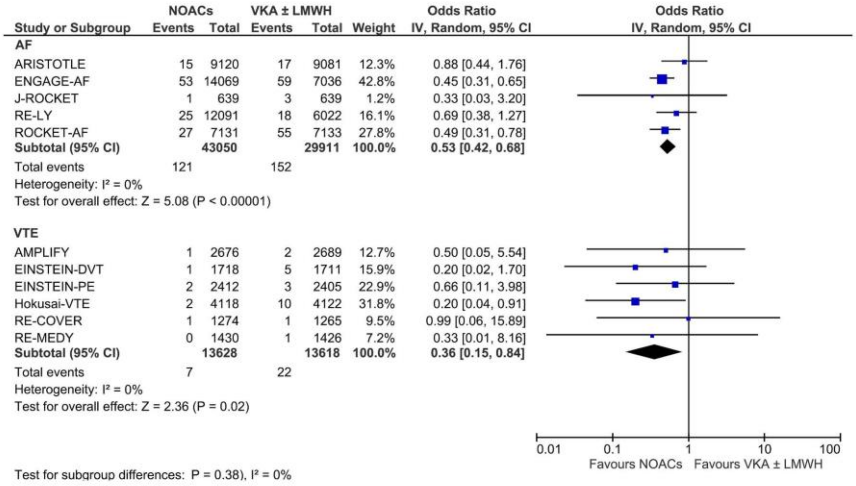

Figure 1 Forest plot of fatal bleeding incidence in comparison with controls according to condition. AF, atrial fibrillation; LMWH, low molecular weight heparin; NOACs, non-vitamin K oral anticoagulants; VKA, vitamin K antagonist; VTE, venous thromboembolism.

the trial sequential α spending monitoring (see online supplementary figure S4).

The number of fatal bleeding events avoided per 1000 patients treated with NOACs was 1 (95% CI 0.2 to 1.4) in an average period of 6 months. Figure 1 shows the forest plot for this outcome.

Major bleeding case fatality rate

Case fatality rate was lower for AF patients treated with NOACs. Pooled analysis showed a significant 32% odds reduction (OR 0.68, 95% CI 0.48 to 0.96; I^2=37%, χ^2=6.38, $P_{heterogeneity}$=0.17) (figure 2). For each 39 patients (95% CI 24 to 322) experiencing a major bleeding event with NOACs, one bleeding fatality is avoided compared with VKAs. Regarding VTE, NOACs did not significantly reduce major bleeding case fatality rate (OR 0.54; 95% CI 0.22 to 1.32; I^2=0%, χ^2=4.05, $P_{heterogeneity}$=0.54) (figure 2).

For both AF and VTE patients, the estimates for major bleeding case fatality were underpowered (72.5% and 33.3% of the required information size for respectively, AF and VTE) (see online supplementary figures S5 and S6). Despite reaching statistical significance, the major bleeding case fatality rate with

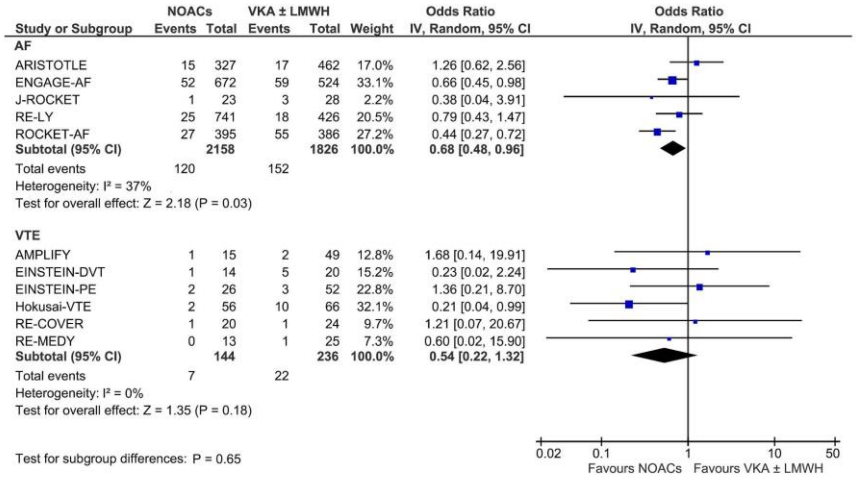

Figure 2 Forest plot of case fatality rate in comparison to controls according to indication. AF, atrial fibrillation; LMWH, low molecular weight heparin; NOACs, non-vitamin K oral anticoagulants; VKA, vitamin K antagonist; VTE, venous thromboembolism.

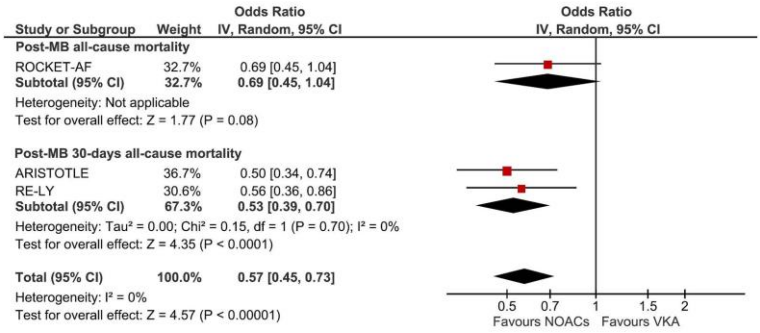

Figure 3 Forest plot of all-cause mortality in major bleeding survivors. NOACs, non-vitamin K oral anticoagulants; VKA, vitamin K antagonist.

NOACs in AF did not cross the trial sequential α spending monitoring boundaries.

Post-major bleeding all-cause mortality

Only AF studies presented data for all-cause mortality following major bleeding events. RE-LY (dabigatran vs VKA)[23] and ARISTOTLE (apixaban vs VKA)[25] provided 30 days post-major bleeding mortality, while ROCKET AF (rivaroxaban vs VKA)[26] data were not limited to the 30 days post-index event. Except for ROCKET AF, data were adjusted for multiple variables. Pooled analysis of these trials showed a significant 43% odds reduction in the risk of all-cause mortality in major bleeding survivors (OR 0.57, 95% CI 0.45 to 0.73; I^2=0%, χ^2=1.22, $P_{heterogeneity}$=0.54) (figure 3). Adjusting the data to the 30 days mortality rate reported by Majeed and colleagues,[S4] 78 deaths (95% CI 63 to 98) would have been avoid per 1000 patients surviving a major bleeding event treated with NOACs compared with VKAs. TSA determined that the minimum information size was 921 patients, and the three trials had 2007 patients experiencing major bleeding events, favouring the robustness of the results.

Outcome results according to NOAC

NOACs were comparable as far as risk of fatal events associated with major bleeding is concerned, either for AF or VTE. The odds reductions for all the outcomes presented above were similar among the different NOACs (figure 4).

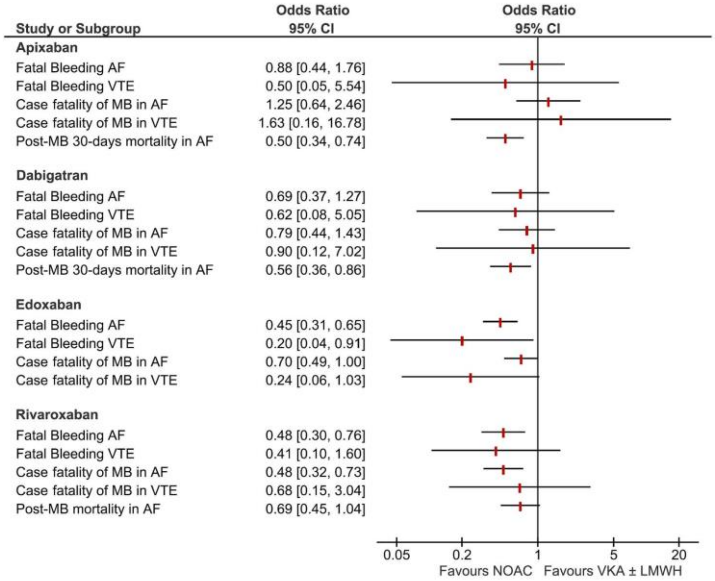

Figure 4 Risk of bleeding-related fatal events according to each NOAC. AF, atrial fibrillation; LMWH, low molecular weight heparin; MB, major bleeding; NOAC, non-vitamin antagonist K oral anticoagulant; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Publication bias

Visual inspection of funnel plot for fatal haemorrhage outcome does not suggest publication bias (see online supplementary figure S7). Egger and Peters regression tests also do not suggest the presence of publication bias in AF population (Egger p=0.60; Peters p=0.71), VTE population (Egger p=0.40; Peters p=0.45) or overall population (Egger p=0.74; Peters p=0.46). For case fatality rates calculation, major bleeding events were used as denominator. Therefore, publication bias evaluation was not reliable. Since only three studies reported postbleeding all-cause mortality, evaluation of the risk of publication bias was not possible for this outcome.

DISCUSSION

The main finding of our study is that NOACs are not associated with an increased mortality. In fact, based on published random controlled data, NOACs decrease the risk of fatal events directly or indirectly related to major bleeding, particularly in AF patients. The figures for VTE failed to reach statistical significance but shared the same trend. Smaller sample sizes and shorter follow-up periods lessen the captured number of major bleeding and fatal events, which probably justifies the lack of significant differences in VTE trials.

Concerns have been raised against NOACs due to the absence of an antidote to reverse anticoagulation in patients with major bleeding events.[S9] In an individual patient the lack of an antidote may interfere with the clinician's perception of available therapeutic options, but most of the studies show that the majority of major bleeding events were managed solely with supportive therapy or red cell transfusion.[23 S4 S5] VKA reversal with vitamin K (used in one-third of major bleeding cases on RE-LY and ROCKET AF trials), fresh frozen plasma (used in 30% and 20% of major bleeding events in RE-LY and ROCKET AF, respectively), prothrombin complex concentrates or recombinant factor VIIa were not frequently used.[23 S4 S5] The underuse of rapid reversal agents raised some concerns as these patients could have been through a suboptimal management, thus resulting in worse outcomes.[S4] These sort of interventions may decrease international normalised ratio (INR) values in VKA-anticoagulated patients, but the best available evidence about the overall effect on active bleeding patients' prognosis lacks robustness.[S10–S12]

Our results highlight the safety of NOACs. These drugs showed inferior rates of fatal bleeding, a lower major-bleeding case fatality rate and a decreased all-cause mortality in bleeding survivors, particularly AF patients. One possible explanation is that the lower mortality is a direct consequence of the reduced risk of intracranial haemorrhage with NOACs—the most feared type of major bleeding event due to its associated morbidity and mortality.[S13 S14] Cerebral vessels haemostasis is likely to be highly dependent on the tissue factor/factor VIIa interaction to primarily initiate the coagulation process. Unlike VKAs, which block the carboxylation process and inhibit the production of functional factor VII, among other coagulation factors, NOACs directly and selectively inhibit factor IIa or Xa without interfering with the primary haemostatic mechanism of cerebral vessels.

Unfortunately, the causes of death among major bleeding event survivors were not ascertained in the clinical trials. Early anticoagulation resumption was associated with a significant decrease of mortality risk in a retrospective cohort of AF patients after a major gastrointestinal bleeding event.[S15] Furthermore, a nested case–control study suggested that early initiation of warfarin was associated with a significant increased risk of stroke during the first 30 days of treatment, probably associated with inadequate anticoagulation.[S16] Owing to the predictability, effectiveness and faster onset of action, patients taking NOACs are probably less likely to experience thrombotic events.[S17] Taking these arguments together, it is reasonable to expect that it contributes to a significantly lower mortality after a major bleeding event.[S17]

Nonetheless, despite the magnitude of the relative risk differences found in our study for the mortality risk reduction, it is important to highlight that fatal bleeding events are uncommon, which translates into low net absolute benefits—one to three events avoided per 1000 treated patients.

For safety concerns, observational studies may be more adequate than RCTs to evaluate safety and drug adverse events, as these may include patients that are usually excluded from RCTs (impaired renal and/or hepatic function) and the follow-up may be longer, enabling the unveiling of unknown adverse events. A retrospective evaluation of the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database revealed that warfarin bleeding reports were more frequent than dabigatran reports, but 15% of dabigatran's bleeding reports were fatal compared with 7.1% of warfarin.[S18] While unadjusted for a balanced comparison, these data are subject to a significant bias of reporting (and adverse events are frequently under-reported). This is particularly relevant in the case of dabigatran and warfarin. Dabigatran is a recent drug and stakeholders are encouraged and motivated to report adverse events in order to increase the knowledge of this drug in real-world conditions. Furthermore, the possibility exists that, in real-world conditions, NOACs may be used in patients significantly different from those included in phase III RCTs. On the other hand, the knowledge of warfarin and its safety profile is well established, which may lead to an under-reporting of these events.

Other observational studies did not report data about bleeding-related fatalities. Regarding major bleeding outcomes, only intracranial haemorrhage risk reduction by dabigatran is supported by real-world data.[S19 S20] The results concerning the risk of overall major bleeding are divergent;[S19 S20] nevertheless, no sign of increased overall mortality was found.[S20] Data about rivaroxaban and apixaban are still scarce, with the follow-up being short and/or inconclusive.[S21–S23]

The most important message of our study relies on the safety of NOACs and the putative protective association regarding major bleeding-related fatality. Therefore, no alert sign of an increased risk of major bleeding-related mortality can be raised.

Limitations

It must be acknowledged that this review includes a meta-analysis of RCTs instead of individual patient data—generating a potential source of bias.

Additionally, heterogeneity of clinical characteristics and interventions/controls across studies should be considered despite the absence of significant statistical heterogeneity and consistency in results. The clinical management of active bleeding patients treated with VKAs had infrequent and suboptimal administration of rapid reversal agents which could have biased the results towards NOACs.

At outcome level, particularly major bleeding case fatality, selective reporting bias is our main concern as NOACs and VKA bleeders have different clinical characteristics and the estimates reported here are unadjusted. Again, it would be necessary to have individual patient data to perform such an analysis. Furthermore, the amount of information/sample size (number

of major bleeders) necessary to adequately evaluate such outcome in a powered fashion was not adequate.

Also for analysis purposes we considered OR to be similar to adjusted HRs assuming a constant rate of events in both arms.

Nevertheless, and despite all limitations, we consider our results robust enough to support the conclusion of the absence of an increased risk of fatal bleeding among NOAC-treated patients.

CONCLUSIONS

Pooled analysis from randomised controlled data shows that NOACs—apixaban, dabigatran, edoxaban, rivaroxaban—significantly decreased the risk of fatal bleeding in patients with AF and VTE compared with VKAs or LMWH followed by VKAs. In patients with AF these drugs were also associated with a significant decreased risk of all-cause mortality in major bleeding survivors. Major bleeding case fatality was also significantly reduced in this context but estimates may be underpowered as the required information size was not reached (72.5% of the required information size).

Despite the absence of specific antidotes, NOACs did not show an increased risk of mortality associated to the bleeding event. Inversely, these drugs were likely to improve these outcomes.

Our results are mere indirect surrogates of the need for NOAC-specific antidotes and studies are ongoing to evaluate the direct efficacy of potential drug-specific antidotes. However, the anticipated cost-effectiveness ratio of these antidotes may preclude its availability in some countries, further making our results relevant for clinical practice.

Key messages

What is already known on this subject?

- Non-vitamin K antagonist oral anticoagulants (NOACs), such as apixaban, dabigatran, edoxaban and rivaroxaban, do not require international normalised ratio (INR) monitoring and are at least as efficacious as vitamin K antagonists (VKAs) in atrial fibrillation (AF) and venous thromboembolism (VTE).
- These drugs decrease the risk of intracranial haemorrhage, but the current lack of availability of a specific antidote is still considered one of the main drawbacks of these drugs.

What might this study add?

- NOACs decrease the risk of fatal bleeding by 47%, major bleeding case fatality (ie, the proportion of fatal events among all major bleeding events) by 32% and all-cause mortality after a bleeding event by 43%.

How might this impact on clinical practice?

- The favourable safety profile and decreased bleeding-related mortality with NOACs compared with VKA anticoagulation support the current approved clinical indications for these medications.

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Contributors DC contributed to the concept and design, data acquisition, data analysis and interpretation of the data; wrote the first draft of the manuscript; critically revised the manuscript; and gave final approval of the submitted manuscript. FR contributed to the interpretation of the data; wrote the first draft of the manuscript; critically revised the manuscript; and gave final approval of the submitted manuscript. MB, ATS, DdA contributed to the data acquisition, data analysis and interpretation of the data; critically revised the manuscript; and gave final approval of the submitted manuscript. NG contributed to the data analysis, and interpretation of the data; critically revised the manuscript; and gave final approval of the submitted manuscript. FJP and JJF contributed to the interpretation of data, critically revised the manuscript and gave final approval of the submitted manuscript. JC contributed to the concept and design, and interpretation of the data; critically revised the manuscript; and gave final approval of the submitted manuscript. DC and JC are the guarantors.

Competing interests JJF had speaker and consultant fees with GlaxoSmithKline, Novartis, TEVA, Lundbeck, Solvay, Abbott, Bial, Merck-Serono, Grunenthal, and Merck Sharp and Dohme; FJP had consultant and speaker fees with Astra Zeneca, Bayer and Boehringer Ingelheim.

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AP&T Alimentary Pharmacology and Therapeutics

Systematic review with meta-analysis: the risk of major gastrointestinal bleeding with non-vitamin K antagonist oral anticoagulants

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SUMMARY

Background
Gastrointestinal (GI) bleeding is a common complication among anticoagulated patients. Non-vitamin K antagonist oral anticoagulants (NOACs) are associated with increased risk of GI (major and clinically relevant non-major) bleeding. However, more information is needed regarding severe events.

Aim
To evaluate the risk of NOACs major GI bleeding.

Methods
We searched for phase III randomised clinical trials (RCT) evaluating NOACs (apixaban, dabigatran, edoxaban and rivaroxaban) and reporting major GI bleeding events, in MEDLINE, Cochrane Library, SciELO collection and Web of Science databases (July 2015). Meta-analysis was performed to estimate risk ratio (RR) and 95% confidence intervals (95% CIs). Heterogeneity was assessed with the I^2 test.

Results
A total of 23 studies were included. Among patients with atrial fibrillation, the risk of major GI bleeding was not different between NOACs and vitamin K antagonists (VKA) (RR 1.08, 95% CI 0.85–1.36, I^2 = 78%; 5 RCTs) or acetylsalicylic acid (RR 0.78, 95% CI 0.36–1.72; 1 RCT). Similar results were found for patients undergoing orthopaedic surgery and those with venous thromboembolism. NOACs were not found to increase the risk compared to low-molecular-weight heparin (LWMH) alone (RR 1.42, 95% CI 0.55–3.71, I^2 = 7%; 8 RCTs), the sequential treatment with LMWH-VKA (RR 0.77, 95% CI 0.49–1.21, I^2 = 43%; 7 RCTs) or placebo (RR 1.48, 95% CI 0.15–14.84, I^2 = 21%; 2 RCTs).

Conclusion
Despite previous evidence supporting the association of non-vitamin K antagonist oral anticoagulants and overall GI bleeding, non-vitamin K antagonist oral anticoagulants were not associated with increased risk of major GI bleeding compared to other anticoagulant drugs (with known increased risk of these events).

Aliment Pharmacol Ther

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INTRODUCTION

Non-vitamin K antagonist oral anticoagulants (NOACs), also named direct oral anticoagulants (DOACs) or target-specific oral anticoagulants (TSOACs), were recently studied for multiple indications. For patients who require long-term anticoagulation, NOACs (such as apixaban, dabigatran, edoxaban and rivaroxaban) are convenient, dismissing the need of regular checking of haemostatic parameters, unlike the vitamin K antagonists (VKA). Furthermore, NOACs have been shown to reduce the risk of major bleeding in comparison with VKA, in particular intracranial haemorrhage,[1] which is judged by clinicians to be the most serious bleeding adverse event.

Gastrointestinal (GI) bleeding is the most frequent cause of major bleeding accounting for 30–40% of these events[2–5] and some studies have shown an increased risk of GI bleeding among NOAC-treated patients.[6, 7] A previously published systematic review have also associated NOACs with an increased GI major and clinically relevant non-major bleeding risk.[8] However, since further trials have been published, the overall severity of this "class effect" is not known. This requires a comprehensive evaluation of major - rather than clinically relevant - bleeding events. Therefore, we intended to evaluate the risk of major GI bleeding associated with NOACs, through a systematic review with meta-analysis of randomised controlled trials (RCTs).

METHODS

This systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement as per the guidelines.[9] The protocol was published in PROSPERO (http://www.crd.york.ac.uk/PROSPERO/) with registration number CRD42015017455.

Eligibility criteria

For this systematic review, we considered the published RCTs which evaluate patients treated with NOACs (also named DOACs or TSOACs), such as dabigatran, apixaban, edoxaban or rivaroxaban, in comparison with any active or placebo control, and reporting major GI bleeding data.

The primary outcome was major GI bleeding, as defined by each trial. When more than one major bleeding definition was available, data using International Society on Thrombosis and Hemostasis (ISTH) definition were used.[10, 11]

We considered all trials, irrespective of patients' baseline disease, comorbidities, background therapy, NOAC treatment duration or follow-up.

Only phase III RCTs were included to obtain robust data without the bias associated with statistical effects of small size underpowered studies on meta-analysis results.[12–15] Furthermore, we were interested in determining the risk associated with approved NOACs and their commonly used doses.

Information sources

MEDLINE, Cochrane Library, SciELO collection and Web of Science databases (inception to July 2015) were used. MEDLINE and Cochrane Library were searched through OVID interface. SciELO collection and Web of Science databases were searched through Web of Science platform. Search strategy is outlined in the Supplementary Online.

Reference lists of systematic reviews, as well as the reference list of included studies were comprehensively searched. As a conventional search may not detect GI bleeds because they may not be mentioned in the title or abstract in the electronic record (although they appear in the full report),[16, 17] we sought for bleeding data in all published phase III RCTs and available public reports of these drugs in the websites of regulatory entities (U.S. Food and Drug Administration, European Medicines Agency and Australian Therapeutic Goods Administration)[18, 19] irrespective of the initial search.

Study selection

After excluding duplicated records obtained in the electronic search, the references were screened independently by two authors through title and abstract for full-text assessment eligibility.

Study characteristics and results were extracted into a standardised form. Included studies were appraised for methodological bias risk with Cochrane Collaboration's Risk of Bias Tool outcomes.[20] Studies were not excluded *a priori* on the basis of quality reporting assessment.

Outcome measures

The primary outcome was GI major bleeding as defined by the ISTH.[10, 11] Other GI bleeding events, not referred or classified as major bleeding, were not included. Outcome data were summarised as dichotomous data.

Data analysis

We used RevMan 5.3.5 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) for statistical

analysis and to derive forest plot showing the results of individual studies and pooled analysis. Intention-to-treat samples were used for this purpose.

We compared NOACs with controls (active drugs or placebo) through random effects meta-analysis to estimate pooled risk ratio (RR) and 95% confidence intervals (95% CIs). The effect measurement estimate chosen was RR because relative measures are more similar across studies with different designs, populations and lengths of follow-up compared to absolute measures, such as risk difference.[21]

Heterogeneity was determined through the chi-squared test. The results were considered heterogeneous if $P < 0.10$. Heterogeneity was further quantified as the percentage of total variation between studies due to heterogeneity through the I^2 test.[22] We used random effects model irrespective of the existence of substantial heterogeneity between study results ($I^2 \geq 50\%$) because we pooled results of studies with different designs and patient characteristics. When significant differences were found, we also determined the number needed to treat or harm (NNT/NNH) and 95% CI, taking into account the control baseline risk. A subgroup analysis was performed with patients who required VKA irrespective of the low-molecular-weight heparin (LMWH) need. Such analysis included patients with atrial fibrillation (AF) and venous thromboembolism (VTE). Pooled estimates for each single NOAC were also retrieved.

Publication bias was assessed through Egger's and Peters' regression tests.[23, 24] Visual evaluation of funnel plot asymmetry was also performed.

RESULTS

Results of the search and included studies

A total of 23 studies fulfilled the eligibility criteria.[6, 7, 20, 25–44] The flowchart of study selection is depicted in Figure S1. Included studies evaluated the risk of major GI bleeding associated with NOACs against VKA ($n = 5$), acetylsalicylic acid (ASA) ($n = 1$), LMWH and VKA ($n = 7$), LMWH alone ($n = 8$) and placebo ($n = 2$).

Risk of major GI bleeding was assessed through ISTH criteria in patients with AF ($n = 6$), VTE ($n = 9$) and patients undergoing total knee replacement ($n = 8$), in a total of 139 585 patients with a mean age ranging from 55 to 73 (Table 1).

Most of the studies included in the analysis were classified as having an overall low risk of bias. However, a few studies (the EINSTEIN acute DVT, the EINSTEIN-PE and the RE-LY study) were open-label RCTs, and consequently allocation concealment procedures and blinding of participants and study personnel items were considered to be of high risk of bias (Figure S2).

Main analyses

Six RCTs evaluated patients with AF, five of which compared NOACs with VKA[6, 7, 25, 27, 28] in 72 961 patients, and one compared NOAC (apixaban) with ASA[26] in 5599 patients. NOACs were not associated with an increased risk of major GI bleeding in comparison with VKA (RR 1.08, 95% CI 0.85–1.36, $P_{heterogeneity} = 0.001$, $I^2 = 78\%$) and ASA (RR 0.78, 95% CI 0.36–1.72).

Seven RCTs evaluated a total of 29 829 patients with VTE and compared NOACs to VKA (with or without the initial treatment with LMWH). Major GI bleeding risk was not different between NOACs and LMWH-VKA (RR 0.77, 95% CI 0.49–1.21, $P_{heterogeneity} = 0.11$, $I^2 = 43\%$).

Eight RCTs compared NOACs with LMWH in 27 371 patients undergoing major orthopaedic surgery (hip or knee replacement) for the prevention of thrombotic events. Major GI bleeding risk of NOACs was not significantly different from LMWH (RR 1.42, 95% CI 0.55–3.71, $P_{heterogeneity} = 0.37$, $I^2 = 7\%$).

Compared to placebo in the extended period of VTE trials (3825 patients), the GI bleeding risk was also not different (RR 1.48, 95% CI 0.15–14.84, $P_{heterogeneity} = 0.27$, $I^2 = 21\%$).

Figure 1 shows the results of the pooled analysis of major GI bleeding risk associated with NOACs, according to the indication for anticoagulation and control group.

Secondary analyses

NOACs vs. VKA (with or without LMWH). Overall, NOACs were compared to VKA (± LMWH) in 12 RCTs enrolling 102 729 patients with AF or VTE, without differences in the pooled major bleeding risk (RR 0.97, 95% CI 0.78–1.21, $P_{heterogeneity} < 0.001$, $I^2 = 66\%$; Figure 2).

Risk of major GI bleeding with individual NOACs. Figure 3 shows the results for each individual NOAC according to the control group. None of the NOACs individually were associated with an increased risk of major GI bleeding.

Publication bias

Asymmetry of study distribution suggested increased risk of publication bias, detrimental to NOAC results

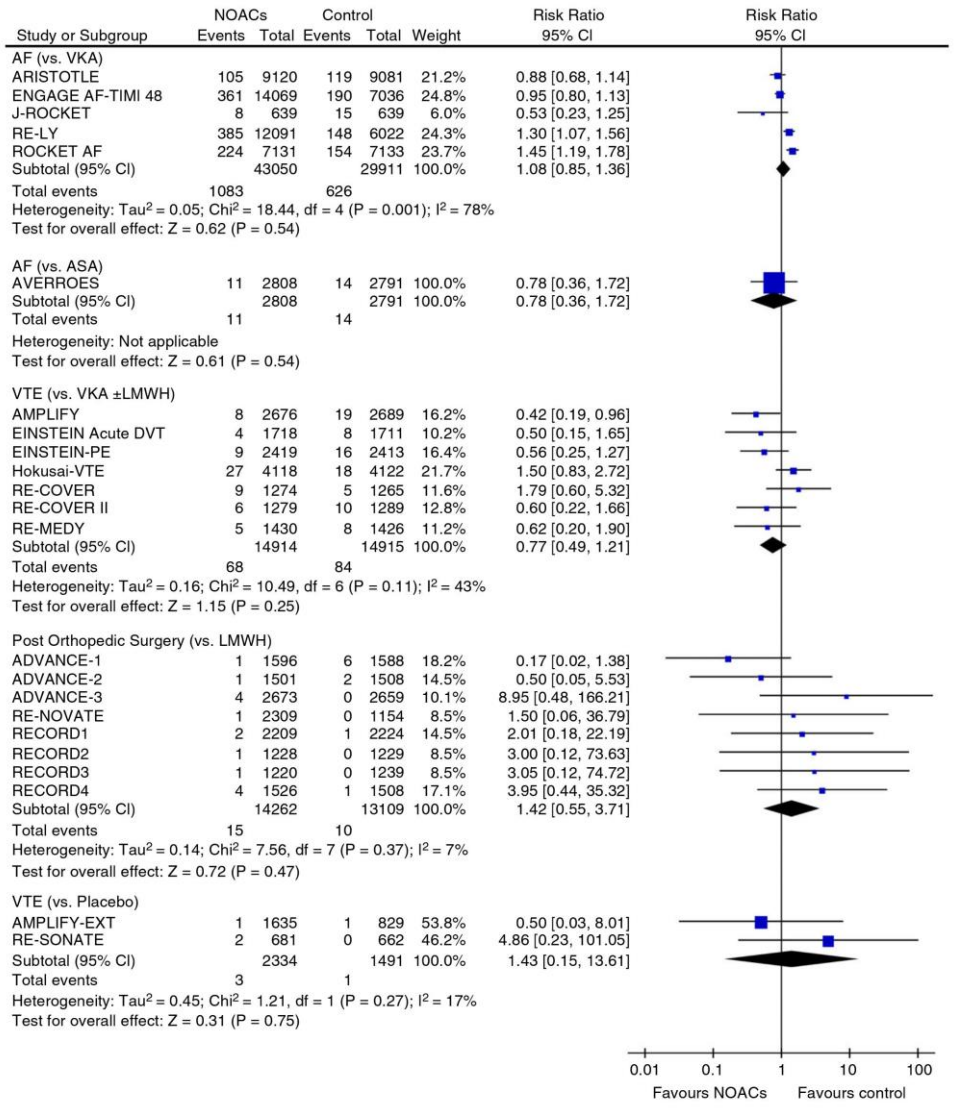

Figure 1 | Forest plot with the results of the pooled analysis for major gastrointestinal bleeding risk associated with non-vitamin K antagonist oral anticoagulants (NOACs), according to the indication and control group. Squares represent the point estimates for individual trials and diamonds represent the results of the meta-analysis. The horizontal lines and the width of the diamond represent the confidence intervals of individual studies and pooled estimates respectively.

Table 1 | Global characteristics of included studies according to clinical indication

Study acronym	Mean age	NOAC group	Control group	Follow-up	Primary outcome
Atrial fibrillation					
ARISTOTLE[27]	70	9120 patients Apixaban 5 mg b.d.	9081 patients dose-adjusted warfarin o.d. Target INR 2.0–3.0	1.8 years	Stroke or systemic embolism
AVERROES[26]	70	2808 patients Apixaban 5 mg b.d.	2791 patients ASA 81–324 mg/day	1.1 years	Stroke or systemic embolism
ENGAGE-AF[28]	72	7035 patients Edoxaban 60 mg o.d.; 7034 patients Edoxaban 30 mg o.d.	7036 patients Warfarin o.d. Target INR 2.0–3.0	2.8 years	Stroke or systemic embolism
J-ROCKET[25]	71	639 patients Rivaroxaban 15 mg o.d.	639 patients Warfarin o.d. Target INR 2.0–3.0; except >70 years INR 1.6–2.6	30 days	Stroke or systemic embolism
RE-LY [6]	72	6015 patients Dabigatran 110 mg b.d.; 6076 patients Dabigatran 150 mg b.d.	6022 patients Warfarin o.d. Target INR 2.0–3.0	2 years	Stroke or systemic embolism
ROCKET-AF [7]	73	7131 patients Rivaroxaban 20 mg o.d.	7133 patients Warfarin o.d. Target INR 2.0–3.0	23 months	Stroke or systemic embolism
Venous thromboembolism					
AMPLIFY[29]	57	2676 patients Apixaban 10 mg b.d. for 7 days, and then 5 mg b.d. for 6 months	2689 patients Enoxaparin, followed by VKA Target INR 2.0–3.0	6 months	Symptomatic recurrent VTE or VTE-related death
AMPLIFY-EXT[44]	57	840 patients Apixaban 2.5 mg b.d.; 813 patients Apixaban 5 mg b.d.	829 patients Placebo	1 year	Symptomatic recurrent VTE or VTE-related death
EINSTEIN Acute DVT[31]	56	1718 patients Rivaroxaban given 15 mg b.d. for 3 weeks, followed by 20 mg o.d.	1711 patients Enoxaparin and VKA Target INR 2.0–3.0	According to intended treatment duration: 3 months (12%), 6 months (63%) and 1 year (25%)	1 Recurrent VTE
EINSTEIN–PE[30]	58	2419 patients Rivaroxaban given 15 mg b.d. for 3 weeks, followed by 20 mg o.d.	2413 patients Enoxaparin and VKA Target INR 2.0–3.0	According to intended treatment duration: 3 months (5%), 6 months (57%) and 1 year (38%)	Symptomatic recurrent VTE
Hokusai-VTE[34]	56	4118 patients Edoxaban 60 mg o.d. or 30 mg o.d. if CrCl 30–50 mL/min or <60 kg	4122 patients Warfarin o.d. Target INR 2.0–3.0	A safety follow-up visit approximately 1 month after the last study drug dose	Recurrent symptomatic VTE
RE-COVER[32]	55	1274 patients Dabigatran 150 mg b.d.	1265 patients Warfarin o.d. Target INR 2.0–3.0	30 days	6-month incidence of recurrent symptomatic VTE and VTE-related death

Table 1 | (Continued)

Study acronym	Mean age	NOAC group	Control group	Follow-up	Primary outcome
RE-COVER II[33]	55	1279 patients Dabigatran 150 mg b.d.	1289 patients Warfarin o.d. Target INR 2.0–3.0	30 days	6-month incidence of recurrent symptomatic VTE and VTE-related death
RE-MEDY[35]	55	1430 patients Dabigatran 150 mg b.d.	1426 patients Warfarin o.d. Target INR 2.0–3.0	6 months	Recurrent symptomatic VTE or VTE-related death
RE-SONATE[35]	56	681 patients Dabigatran 150 mg b.d.	662 patients Placebo	18 months	Recurrent symptomatic VTE or VTE-related death or all-cause mortality
Post-surgical prophylaxis of VTE					
ADVANCE-1[36]	66	1596 patients Apixaban 2.5 mg of b.d.	1588 patients Enoxaparin 30 mg b.d.	60 days after anticoagulation period	DVT, nonfatal pulmonary embolism, and all-cause mortality
ADVANCE-2[37]	67	1501 patients Apixaban 2.5 mg of b.d.	1508 patients Enoxaparin 40 mg o.d.	60 days after anticoagulation period	DVT, non-fatal pulmonary embolism, and all-cause mortality
ADVANCE-3[38]	61	2673 patients Apixaban 2.5 mg of b.d.	2659 patients Enoxaparin 40 mg o.d.	60 days after anticoagulation period	DVT, non-fatal pulmonary embolism or all-cause mortality
RECORD1[40]	63	2209 patients Rivaroxaban 10 mg o.d.	2224 patients Enoxaparin 40 mg o.d.	30–35 days after the last dose of study medication	DVT, non-fatal pulmonary embolism or all-cause mortality
RECORD2[41]	62	1228 patients Rivaroxaban 10 mg o.d.	1229 patients Enoxaparin 40 mg o.d.	30–35 days after the last dose of study medication	DVT, non-fatal pulmonary embolism, and all-cause mortality
RECORD3[42]	68	1220 patients Rivaroxaban 10 mg o.d.	1239 patients Enoxaparin 40 mg o.d.	30–35 days after the last dose of study medication	DVT, non-fatal pulmonary embolism or all-cause mortality
RECORD4[43]	65	1526 patients Rivaroxaban 10 mg o.d.	1508 patients Enoxaparin 30 mg b.d.	30–35 days after the last dose of study medication	DVT, non-fatal pulmonary embolism or all-cause mortality
RE-NOVATE [39]	64	1146 patients Dabigatran 220 mg of o.d.; 1163 patients Dabigatran 150 mg o.d.	1154 patients Enoxaparin 40 mg o.d.	60 days after coagulation period	VTE events and VTE-related death

AF, atrial fibrillation; ASA, acetylsalicylic acid; b.d., twice daily; CrCl, creatinine clearance; DVT, deep-vein thrombosis; INR, international normalised ratio; o.d., once daily; VKA, vitamin K antagonists; VTE, venous thromboembolism.

(Figure S3). A balanced funnel plot would further favour results towards a decreased risk of major GI bleeding with NOACs which is supportive of the safety of these drugs. Nevertheless, Egger ($P = 0.47$) and Peters' ($P = 0.11$) tests do not support increased risk for publication bias.

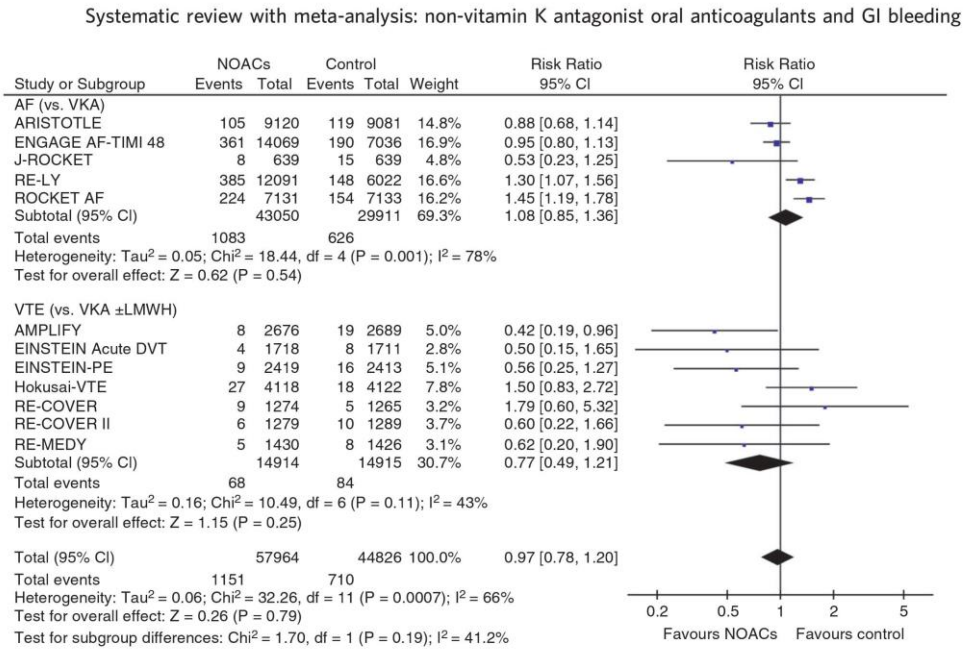

Figure 2 | Forest plot with the results of the pooled analysis for major gastrointestinal bleeding risk associated with non-vitamin K antagonist oral anticoagulants (NOACs) vs. vitamin K antagonists (VKA) [with or without low-molecular-weight heparin (LMWH)]. Squares represent the point estimates for individual trials and diamonds represent the results of the meta-analysis. The horizontal lines and the width of the diamond represent the confidence intervals of individual studies and pooled estimates respectively.

DISCUSSION

The main conclusion of this systematic review is that NOACs, overall, did not increase the risk of major GI bleeding. Even with the established proneness to GI bleeding associated with NOACs, our data suggest that it is not due to severe events. This conclusion derives from phase III randomised controlled data. This is a considerable contribution to previously published data[8] due to the inclusion of more recent trials, and restriction of analysis to major GI bleeding.

NOACs have an oral route of administration and, with the exception of dabigatran, all of them may have their anticoagulant effect directly in the mucosa of the gut. Dabigatran etexilate is a prodrug, and is converted into the active metabolite by esterases present in the gut, plasma and liver. Moreover, dabigatran's oral route bioavailability is 7% and the remainder may act locally in the absorption site.[45] Therefore, dabigatran can also have a direct anticoagulant effect in the mucosa, but these pathophysiologic mechanisms require scientific support.

Different from NOACs, LMWH have a parenteral route and do not have a tropism for or a direct effect on the GI tract. VKAs have an oral route but the anticoagulant effect is dependent on the hepatic inhibition of vitamin K epoxide reductase, to block the function of coagulation factor II, VII, IX and X.[46] This means that both LMWH and VKA would concurrently need other conditions to provoke a major GI bleed. Our data emphasise the safety of NOACs in terms of major GI bleeding compared to VKA[47] and other anti-thrombotic drugs.

Trials with AF patients had higher incidence of GI bleeding (major GI bleeding incidence with NOACs in patients with AF was 2.5%, while 0.5% of VTE patients experienced this event) compared to other conditions evaluated here. These data are concordant with the comment of Beyer-Westendorf which claimed that AF patients are known to have higher bleeding rates, because they are older, have more comorbidities and concomitant anti-platelet drugs, and AF trials are

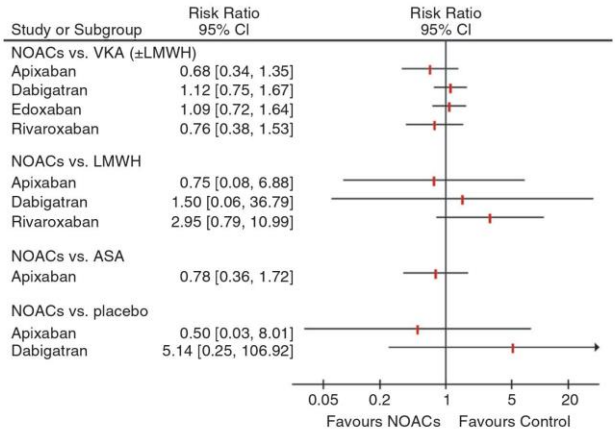

Figure 3 | Results of pooled analyses according to each individual non-vitamin K antagonist oral anticoagulant (NOAC). The central markers represent the point estimates the meta-analysis for each NOAC according to comparator, irrespective of the baseline condition.

generally longer than VTE trials, increasing the probability to capture more events.[48]

Therefore, the main studies to understand the details involved in major GI bleeding are those with AF patients. The RE-LY trial, which evaluated dabigatran vs. warfarin in patients with AF, was the most comprehensive regarding GI adverse events.[49] In a *post hoc* evaluation, dabigatran showed an increased risk of non-bleeding upper GI adverse events, but no difference from warfarin was found in terms of any severe GI adverse events. In fact, dabigatran had numerically less severe adverse events than warfarin. These upper GI symptoms were present in one-third of GI bleeding events. The gastroduodenal injury on endoscopy was expectably associated with increased risk of bleeding (RR 6.92, 95% CI 5.49–8.72). Oesophageal injury should also be considered as 20% of patients treated with dabigatran with GI symptoms referred to endoscopy, may have oesophageal mucosal ulceration.[50] Data for proton pump inhibitors (PPI) used to improve GI care in patients treated with NOACs are heterogeneous. In RE-LY, PPI were not associated with a decrease in the risk of these events, possibly due to previous GI symptoms that required these drugs.[49] However, gastroprotective drugs (41% treated with PPI) were associated with decreased GI bleeding risk in a retrospective cohort with approximately 5000 patients treated with dabigatran.[51] As expected, ASA or non-steroidal anti-inflammatory drugs (NSAIDs) were associated with major bleeding events, irrespective of the anticoagulant treatment (NOAC or VKA).[4, 52] Therefore, drugs that have potential pharmacodynamic interactions with anticoagulants, such as ASA or NSAIDs, should be withdrawn whenever possible.

In patients who started dabigatran or switched from VKA to dabigatran, the results were heterogeneous.[53, 54] A *post hoc* analysis of RE-LY using the adjusted estimates of the European label for dabigatran showed a trend towards increased risk of GI bleeding.[55]

In a propensity-matched evaluation of dabigatran and warfarin-treated in the Danish Registry,[56] there was an association between dabigatran 110 mg and a lower risk of GI bleeding [hazard ratio (HR) 0.60, 95% CI 0.37–0.93], and risk was similar compared to warfarin with both dosages in patients with exposures >1 year.[56] On the other hand, a Medicare retrospective study showed that dabigatran (without specification of doses) significantly increased risk of any major bleeding irrespective of the bleeding site (HR 1.58, 95% CI 1.36–1.83).[57]

Despite the heterogeneity, three recently published cohort studies did not find any association between NOACs exposure and GI bleeding,[58–60] with the exception of elderly patients in one of the studies.[60]

Thus, the heterogeneity in the results of the current published post-marketing large cohort studies precludes a definite answer for this question.

Limitations

This review includes a meta-analysis of RCTs and not individual patient data, which is a potential source of bias. Search methods are based on published RCTs. Multiple databases were searched, but some like EMBASE were not available to the authors. To partially exceed this limitation, the authors explored all NOAC published phase III RCTs and systematic reviews for data of interest.

Included studies were not powered to detect differences in major GI bleeding risk and the incidence of major GI bleedings was relatively low (<3% in studies with longer follow-up); therefore, results should be interpreted carefully. Despite the potential limitations inherent in the inclusion of phase II trials (mentioned in Methods), their exclusion may increase the risk of bias and should be acknowledged.

Heterogeneity of clinical characteristics and interventions (different NOACs, the same NOAC at different dosages, and the possibility of different co-medications, such as anti-platelet drug which are commonly associated with GI bleeding) across various studies should also be considered. The statistical heterogeneity found in some subgroups defined according to the control group used in the trial is a further limitation. The outcome of interest was major GI bleeding according to the ISTH definition.[10, 11] All trials that were included reported major bleeding events according to the ISTH definition (for medical or surgical conditions, or modified ISTH definitions). Nevertheless, it is not possible to evaluate whether these small variations may have an impact on the final results.

CONCLUSION

In patients requiring anticoagulation, there is no evidence of increased risk for major GI bleeding with the NOACs compared to other anti-thrombotic drugs, which, themselves are associated with a definite risk of major GI bleeding. However, the lack of power of the included studies and the scarcity of events, as well as the possible bias from other concomitant anti-thrombotic drugs, preclude a definitive conclusion. It is particularly important to evaluate as to whether these findings from a random-controlled setting are also documented in real-life post-marketing studies.

AUTHORSHIP

Guarantor of the article: Daniel Caldeira.

Author contributions: DC contributed to the concept and design, data acquisition, data analysis and interpretation of the data, wrote the first draft of the manuscript, and critically revised the manuscript. MB, AF, AR and AA contributed to data acquisition and data analysis, wrote parts of the manuscript and critically revised it. FJP, JC and JJF contributed to the interpretation of data and critically revised the manuscript.

All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Data S1. Search strategy.

Figure S1. Flowchart of studies selection.

Figure S2. Risk of bias evaluation. The green symbols represent low risk of bias, the yellow symbols represent unclear risk of bias and the red symbols represent high risk of bias.

Figure S3. Funnel plot. Intervention effect estimates from individual studies are plotted against their precision.

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REVIEW

Intracranial hemorrhage risk with the new oral anticoagulants: a systematic review and meta-analysis

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Abstract The new oral anticoagulants/non-vitamin K antagonists oral anticoagulants (NOACs) have recently reached the market and less is known about their safety in comparison to their efficacy. Therefore, we aimed to evaluate intracranial hemorrhage (ICH) risk with NOACs, the most feared adverse event of anticoagulation treatment. This is a systematic review and meta-analysis of phase III randomized controlled trials (RCTs) comparing NOACs versus any control and reporting ICH events. Studies were searched through Medline and Cochrane Library (April 2014). Reviews and reference lists were also screened. Random effects' meta-analysis was performed to derive pooled estimates expressed as relative risk (RR) and 95 % CI. Number needed to treat/harm (NNT/NNH) taking into account the baseline risk was also calculated. Heterogeneity was evaluated with I^2 test. 18 RCTs evaluating 148,149 patients were included. NOAC significantly reduced ICH risk compared to vitamin K antagonists (VKA) (RR 0.44; 95 % CI 0.36–0.54; $I^2 = 37$ %; NNT: 137 during 2 years) and to sequential treatment with low molecular weight heparin and VKA (RR 0.28; 95 % CI 0.12–0.65; $I^2 = 0$ %; NNT: 463 patients during 7 months). Compared to placebo, NOACs were associated with an increased ICH risk (RR 3.31; 95 % CI 1.59–6.90; $I^2 = 0$ %; NNH: 433 during 1 year). Results were similar for the different NOAC drugs and across the different clinical conditions. In patients requiring anticoagulation treatment, the risk of ICH is about half with the NOACs in comparison to standard antithrombotic treatment. This safer profile found in RCTs should be confirmed in real-world database studies.

Keywords Intracranial hemorrhages · Anticoagulants · Meta-analysis

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Introduction

Oral anticoagulants are the corner stone therapeutic option for the prevention and/or treatment of venous thromboembolism and atrial fibrillation. The so-called new oral anticoagulants (NOACs) or non-vitamin K oral anticoagulants selectively inhibit factors IIa or Xa. These drugs have overcome some limitations associated with the

traditional oral and parenteral anticoagulants. In randomized controlled trials (RCTs), it has been shown that NOACs' efficacy across a whole spectrum of prothrombotic conditions is, at least, non-inferior to the standard care [1].

Regarding safety, it is not surprising that anticoagulants pose an increased risk of bleeding [2]. Among the many possible different bleeding events, both in terms of location and severity, intracranial hemorrhage (ICH) is by far the most feared due to the increased morbidity and lethality [3, 4]. In RCTs, NOACs' risk of major bleeding events has been heterogeneous [5, 6], and uncertainty exists regarding a putative "protective" effect of NOACs in comparison to other antithrombotic drugs through all indications, as well as the clinical relevance of this effect. Therefore, we aimed to evaluate these questions by performing a systematic review of RCTs evaluating NOACs ICH risk irrespective of the indications under study.

Methods

Guidelines

Preferred reporting items for systematic reviews and meta-analyses (PRISMA) framework guidelines were used for reporting guidance [7].

Studies' eligibility criteria

For this review, we included all phase III RCTs comparing NOAC, namely direct inhibitors of IIa (dabigatran) or Xa (apixaban, darexaban, edoxaban, or rivaroxaban), with any other control group (placebo, no-treatment or standard care, non-pharmacological interventions or any drug), reporting data for ICH events. We selected only phase III RCTs because we were interested in determining the risk associated with the approved and commonly used doses of the NOACs. Furthermore, we wanted to avoid bias in risk estimation due to statistical effects of rare events and the impact of small-size underpowered studies on meta-analysis results [8–11]. All RCTs were considered for inclusion irrespective of patients' indications for anticoagulation.

Search method

Investigators retrieved potential-eligible studies through an electronic search in Medline (via OVID) and Cochrane Library, performed in April 2014. Search strategy is detailed in supplementary online. There were no language restrictions. Additionally, we checked the references of retrieved systematic reviews and meta-analyses that evaluated NOAC, as well as the reference list of each included study. When data for the intended outcome were not available from published articles, we looked at the available public reports of these drugs from the European Medicine Agency and Food and Drug Administration websites.

Data extraction, evaluation and synthesis

Titles and abstract of obtained records were screened independently by two authors. Doubts and disagreements were solved by consensus. Selected studies were assessed in full-text to determine the appropriateness for inclusion in the systematic review. Study characteristics and outcomes were extracted independently by two authors.

Appraisal of methodological bias was done according to the Cochrane Collaboration's tool for assessing risk of bias [12]. Studies were not excluded a priori based on their quality of reporting.

Statistical analysis

We aimed to estimate the incidence of ICH (primary outcome), defined as any intra-axial or extra-axial hemorrhage diagnosed and reported by investigators as such. Data from each study were treated as dichotomous data. Risk ratio (RR) and 95 % confidence interval (95 % CI) were used to report data from pooled results because relative measurements, such as RR, are more similar across studies with different designs, populations, baseline risk and lengths of follow-up, than absolute measurements of treatment effect [13]. In the presence of significant differences between groups, we also calculated the number needed to treat/harm (NNT/NNH) and 95 % CI taking into account the baseline risk (weighted proportion of bleeding event rate in control group) because of possible differences in the predicted absolute effect of treatment according to variation in baseline risk between groups [14, 15].

Software Review Manager 5.2.6 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) was used to obtain the estimates of individual studies, pooled analysis and to retrieve the forest plots. Heterogeneity was assessed with the I^2 test, which measures the percentage of total variation attributed to inter-study heterogeneity rather than random [16]. The inverse of variance method with random effects' model was used by default independently of the existence ($I^2 \geq 50$ %) or not of substantial heterogeneity between studies' results.

We assumed that the risk of ICH is above all a direct consequence of the drug itself (described in clinical trials as treatment-emergent or treatment-related adverse events), and therefore, NOAC-associated ICH risk should not be significantly different across the clinical conditions in which these drugs are used. Consequently, in the primary

analysis we decided to pool the data for NOAC according to the control group used (active drug or placebo/no-treatment) and not according to the clinical condition in which they were evaluated. However, to explore whether the ICH risk was different across individual NOACs and in particular clinical conditions, we performed a subgroup analysis based on each individual NOAC and clinical conditions, irrespectively of the presence or not of significant heterogeneity found in the primary analysis.

Publication bias was assessed through visual inspection of funnel plot asymmetry and with Egger's and Peters' regression tests [17, 18].

Results

The study selection for this review returned 18 RCTs reporting at least one ICH event (supplementary Fig. 1) [19–36]. The included trials evaluated NOAC among different clinical conditions and settings: patients with venous thromboembolic disease (VTD) ($n = 6$ RCTs), non-valvular atrial fibrillation (NVAF) ($n = 6$ RCTs), acute coronary syndrome ($n = 2$ RCTs), patients that underwent orthopedic surgery ($n = 2$ RCTs) and patients hospitalized for medical illnesses ($n = 2$ RCTs).

These 18 studies evaluated a total of 148,149 patients with a mean age ranging from 55 to 73 years. The comparators were different according to the different settings: low molecular weight heparin (LMWH) after orthopedic surgery ($n = 2$ RCTs), LMWH–VKA sequential combination in VTD disease ($n = 4$ RCTs), VKA ($n = 6$ RCTs) and acetylsalicylic acid (ASA) ($n = 1$ RCT) in NVAF, LMWH–placebo in patients with medical illnesses ($n = 2$ RCTs), and placebo in acute coronary syndrome (ACS) and VTD trials ($n = 3$ RCTs).

Overall, the risk of bias of included studies was considered to be low (supplementary Fig. 2).

ICH risk associated with NOACs in comparison to controls

The forest plot with the pooled analysis of ICH risk associated with NOACs according to each control group is illustrated in Fig. 1.

NOACs were compared to LMWH in two RCTs evaluating apixaban and rivaroxaban on 6,218 patients that underwent surgery (knee or hip). ICH risk was similar between NOAC and LMWH with an RR of 0.33 (95 % CI 0.03–3.18; $I^2 = 0$ %; Fig. 1) during a mean treatment period of 1.5 months.

In comparison to sequential treatment with LMWH and VKA among patients with VTD ($n = 4$ RCTs; 20,961 patients), NOACs were associated with a significant 72 % risk reduction of ICH risk (95 % CI 35–88 %; Fig. 1), without statistical heterogeneity ($I^2 = 0$ %). NNT to prevent one ICH compared to LMWH–VKA was 463 patients during an average of 7 months.

VKA were the comparators of choice in almost all RCTs evaluating patients with NVAF and in one RCT in patients with VTE [28]. Pooled analysis ($n = 6$ RCTs; 75,649 patients) showed a significant 56 % ICH risk reduction (95 % CI 46–64 %; Fig. 1), with low-to-moderate statistical heterogeneity ($I^2 = 37$ %). NNT was 137 patients during 2.1 years on average. Sensitivity analysis by excluding RE-MEDY trial (which enrolled patients with VTE) yielded similar results (RR 0.44; 95 % CI 0.35–0.55; $I^2 = 49$ %; Fig. 1) [28].

AVERROES was the only RCT that compared NOAC (apixaban) with ASA in patients with atrial fibrillation unsuitable for VKA treatment [21]. This trial included 5,599 patients and the ICH RR reported in the trial was 0.84 (95 % CI 0.38–1.87; Fig. 1).

Two RCTs evaluated NOACs in 14,399 patients that were hospitalized with medical illnesses and used a short course of LMWH followed by placebo as comparator arm [25, 36]. The use of NOACs in this context was not associated with an increased risk of ICH (RR 1.01, 95 % CI 0.04–23.36; $I^2 = 53$ %; Fig. 1).

NOACs were compared against placebo in one extended study period of an apixaban RCT in patients with post-VTE [24], and in two RCTs with ACS patients [20, 34]. Overall these studies included 25,323 patients. The pooled analysis of these three placebo-controlled trials (ACS and post-VTE setting) showed a significant increase in ICH risk with NOAC (RR 3.31; 95 % CI 1.59–6.90; $I^2 = 0$ %). NNH was 433 patients during approximately 1 year on average.

ICH risk associated with each individual NOAC and clinical condition

Table 1 shows the main results for the subgroup analysis considering each individual NOAC and clinical condition. In comparison to controls, the ICH risk was similarly lower for all individual NOACs and across all studied populations. The only exception was the case of rivaroxaban in medically ill patients [36]. Magellan trial was not powered to evaluate the impact of NOACs in ICH risk on medically ill patients. Study's population also includes patients with very heterogeneous conditions [36]. Furthermore, the bleeding risk in medically ill patients is not well defined, and clinical characteristics could not have been adequately balanced between groups.

For each individual NOAC, the ICH risk reduction was similar across the different populations in which they have

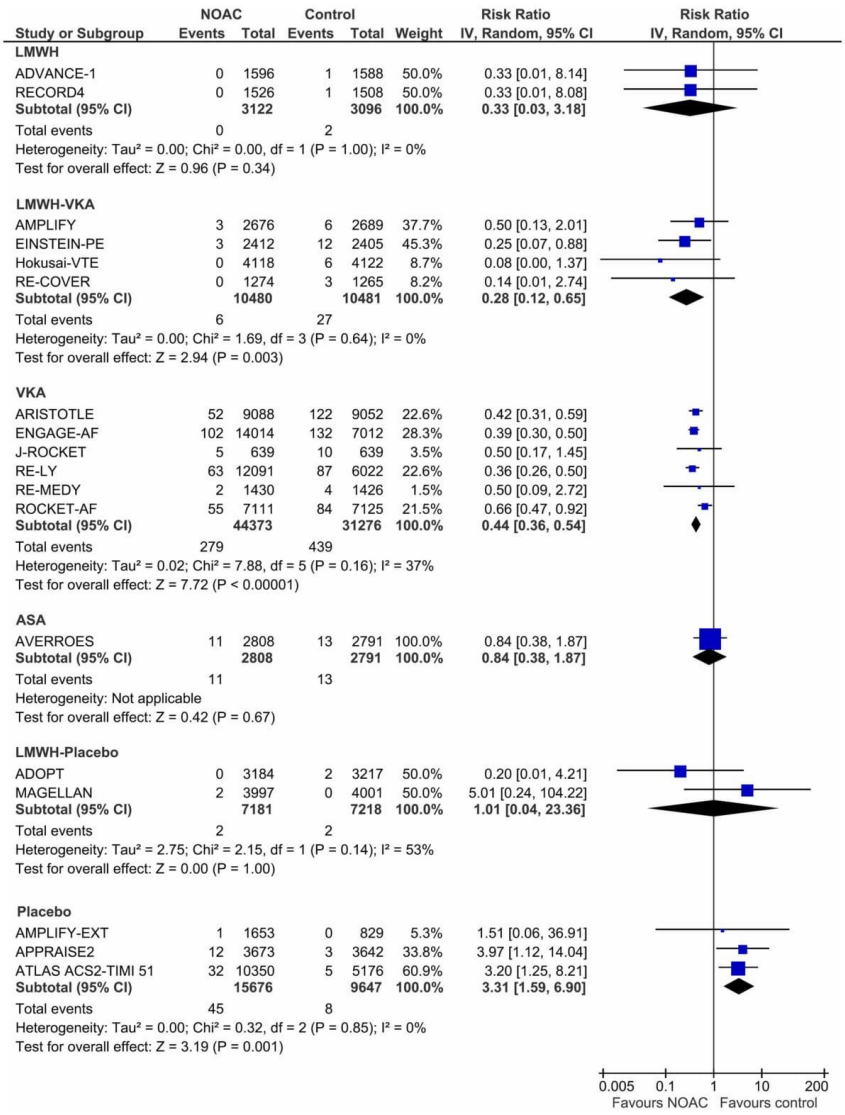

Fig. 1 Risk of intracranial hemorrhage with NOACs in comparison to controls

been tested ($p > 0.25$ for all subgroup differences according to the clinical condition under evaluation; Table 1). In addition, no significant differences existed in ICH risk reduction when considering the different subgroups according to the active control (LMWH, LMWH–VKA, VKA, ASA) ($p = 0.30$ for subgroup differences). Taken together, these findings suggest a drug-class effect and corroborate our initial presupposition that NOAC-

Table 1 Risk of ICH associated with the different NOACs (versus active controls) and clinical conditions

Population	Apixaban			Dabigatran			Edoxaban			Rivaroxaban		
	Studies	RR [95 % CI]	I^2	Studies	RR [95 % CI]	I^2	Studies	RR [95 % CI]	I^2	Studies	RR [95 % CI]	I^2
Medical Ill patients	1 study 6,401 pts	0.20 [0.01, 4.21]	NA	–	–	–	–	–	–	1 study 7,998 pts	5.01 [0.24, 104.2]	NA
Post-surgical prophylaxis	1 study 3,184 pts	0.33 [0.01, 8.14]	NA	–	–	–	–	–	–	1 study 3,034 pts	0.33 [0.01, 8.08]	NA
VTE	1 study 5,365 pts	0.50 [0.13, 2.01]	NA	2 studies 5,395 pts	0.37 [0.08, 1.59]	0 %	1 study 8,240 pts	0.08 [0.00, 1.37]	NA	1 study 4,817 pts	0.25 [0.07, 0.88]	NA
AF	2 studies 2,373 pts	0.54 [0.28, 1.02]	0 %	1 study 18,113 pts	0.36 [0.26, 0.50]	NA	1 study 21,026 pts	0.39 [0.30, 0.50]	NA	2 studies 15,514	0.64 [0.46, 0.88]	0 %
Pooled	5 studies 38,689 pts	0.46 [0.35, 0.62]	0 %	3 studies 23,508 pts	0.36 [0.26, 0.49]	0 %	2 studies 29,266 pts	0.33 [0.14, 0.83]	0 %	5 studies 31,363 pts	0.60 [0.41, 0.87]	5 %
p value for differences across conditions with the same NOAC	0.93			0.99			0.27			0.26		

AF atrial fibrillation; *CI* confidence intervals; *NA* not available; *NOAC* non-vitamin K antagonist oral anticoagulant; *pts* patients; *RR* risk ratio; *VTE* venous thromboembolism

associated ICH risk is mainly a consequence of the drug itself and not of the conditions in which they are used.

Risk of publication bias

Funnel plot was not suggestive of publication bias (supplementary Fig. 3), and both Egger ($p = 0.87$) and Peters ($p = 0.66$) test results were also not suggestive of important publication bias.

Discussion

Intracranial hemorrhage is a well-known serious complication of antithrombotic drugs [37, 38]. The most important finding of this review is the safer profile of the new oral anticoagulants regarding this outcome in comparison to standard antithrombotic strategies and across different clinical conditions. This review also showed, as expected, an increased risk of ICH with NOACs when compared with placebo.

In comparison to other anticoagulant regimens (considered the standard of care in each condition), the risk of ICH was reduced to more than an half with the NOACs, particularly against VKA (mostly in AF patients) and LMWH–VKA (VTD patients) regimens, which owe the most robust data of this review. Treatment with VKA requires INR periodical monitoring, and despite the controlled environment of clinical trials the mean time in therapeutic range did not exceed 70 %. The risk reduction here retrieved (about 70 %) was both clinically and statistically significant, without statistical heterogeneity. The evidence carried from other conditions and other comparators, such as LMWH, was not only smaller, with larger CIs, but also overlaps with the other estimates.

The risk of anticoagulation-related ICH has been previously evaluated and the absolute risk reduction of this outcome was not different across clinical conditions [39]. In line with this conclusion, the results here presented showed a consistent decrease of ICH risk with NOACs compared to active controls. Reliable estimates of ICH events are difficult to retrieve from single-trial results as these are relatively rare events. Despite the methodological limitations of this analysis, the inclusion of multiple large-size trials, the absence of subgroup differences and the estimates consistency provide robustness to the findings.

According to a subanalysis of RE-LY, intracerebral and subdural hemorrhages (46 % each) were the most common types of ICH [40]. Dabigatran significantly decreased the risk of both these types of ICH. Dabigatran also decreased the risk of traumatic ICH (most of them with a subdural location) without increasing the case-fatality rate [40]. A post hoc analysis of ROCKET AF confirmed the protective

effect of rivaroxaban concerning overall ICH through a multivariable cox proportional hazards model [41]. However, rivaroxaban did not reduce ICH-related mortality [41].

These results are important to patients, physicians and policy-makers. NOACs are at least as effective as VKA/LMWH in the studied conditions and significantly decreased ICH risk. Furthermore, NOACs do not require regular control of anticoagulation status, like in the case of VKA-treated patients. Treatment with NOACs waives such burden and lightens resources consumption. NOACs are also likely to be cost-effective, which is of extreme importance for policy-makers [42–44].

Limitations

This systematic review with meta-analysis has limitations related to included studies and analysis method, including the fact of being a study-based meta-analysis rather than individual patient data analysis.

Pooling data from studies evaluating patients with different clinical conditions is always a methodological concern and should be considered as a limitation for conclusions. Other potential limitation is the possibility of selection bias because a significant proportion of patients with AF have already been treated with VKA without previous major bleeding events (exclusion criteria of all trials).

Conclusions

In patients requiring anticoagulation treatment, the risk of ICH is about half with the NOACs in comparison to standard antithrombotic treatment.

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Conflicts of interest DC, MB and JC do not have any conflict of interests to disclose. JJF had speaker and consultant fees with GlaxoSmithKline, Novartis, TEVA, Lundbeck, Solvay, Abbott, Bial, Merck-Serono, Grunenthal, and Merck Sharp and Dohme. FJP had consultant and speaker fees with Astra Zeneca, Bayer and Boehringer Ingelheim.

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Letter to the Editor

Pericardial bleeding risk with non-vitamin K oral anticoagulants: A meta-analysis

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Dear Editor,

We have read with interest the case report by Xu and MacIsaac, which has brought many thoughtful and interesting questions about bleeding challenges with the new antithrombotic drugs [1], particularly the association of one non-vitamin K oral anticoagulant (NOAC), rivaroxaban, with a life-threatening pericardial bleeding.

The NOACs have challenged vitamin K antagonists (VKAs) in some indications. Despite the differences in renal clearance and dosing regimens [2–4], NOACs have a lower risk of intracranial bleeding [5], have predictable dose–response relation dismissing the need of regular evaluation of hemostasis parameters, and are at least as efficacious as VKA for most of the evaluated indications [2].

By pooling data from several similar studies, meta-analysis allows a better estimation of the association between one particular intervention and an outcome, being particularly relevant when uncertainty exists [6] as in the case report published by Xu and MacIsaac. Therefore, we performed a meta-analysis of phase III randomized controlled trials (RCTs) to better estimate the risk of pericardial bleeding with the NOACs.

A database search through Medline and CENTRAL was performed from inception to November 2014. Public reports of NOACs at the European Medicine Agency and Food and Drugs Administration sites were also searched.

Study selection and data extraction were done independently and cross-checked for accuracy. RCTs that reported data on pericardial bleeding events were included for analysis. We excluded all RCTs that did not report pericardial bleeding events or that reported zero events in both arms, because such studies do not provide any indication of either the direction or magnitude of the relative treatment effect [7].

Six VKA-controlled RCTs (1 apixaban [8], 2 dabigatran [9,10], 1 edoxaban [11], and 2 rivaroxaban [12,13]) fulfilled the inclusion criteria. Overall 78,900 patients (45,995 exposed to NOACs and 32,905 exposed to VKA) with non-valvular atrial fibrillation [8,10–12] or venous thromboembolism [8,13] were evaluated in these RCTs. Mean follow-up ranged from 6 months to 2.8 years. In these trials the incidence of reported pericardial bleeding was very low (0.02%). Thus we performed a random effects meta-analysis in order to retrieve NOAC's relative risks (RR) for pericardial bleeding. When only one arm presented zero events a continuity correction (addition of 0.5) was done to adjust data for analysis. Peto's method was not used due the existence of unbalanced arms.

Pooled results for all NOACs did not show an increased risk of pericardial bleeding (RR 0.81; 95% CI: 0.31 to 2.11; Fig. 1). No heterogeneity was noticed across studies estimates ($I^2 = 0\%$). As expected, due to the rare frequency of these events, individual NOACs, depicted in Fig. 2, were not associated to an increased or decreased risk of pericardial bleeding ($p = 0.49$ for subgroup differences).

This method has limitations including the fact of being a study-based meta-analysis and not an individual patient-data analysis. In the ARISTOTLE trial, no events were reported during the on-treatment period. The only event occurred in a patient randomized to apixaban more than 3 days after drug discontinuation. Still, we have included this event to be as conservative as possible.

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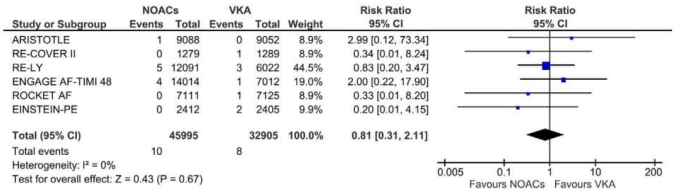

Fig. 1. Forest plot of pericardial bleeding risk with NOACs.

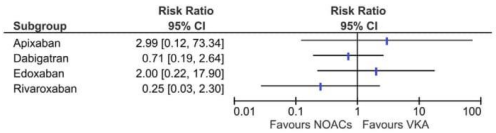

Fig. 2. Results for individual NOACs.

In conclusion, pericardial bleeding may be life-threatening but it is a very rare clinical event. Based on the best available evidence, no safety alert can be raised for an increased risk of pericardial bleeding with NOACs (including rivaroxaban). However, it is pharmacologically reasonable to expect that patients exposed to anticoagulation (including NOACs) and other drugs, such as antiplatelet and non-steroid anti-inflammatory agents, may be at a higher risk of bleeding events due to pharmacodynamic drug interactions. As usually occurs with recent approved drugs, post-marketing surveillance monitoring should be warranted in order to consolidate or jeopardize these results.

Conflict of interest

DC, MB, NG, and JC do not have any competing interests to disclose. JJF had speaker and consultant fees with GlaxoSmithKline, Novartis, TEVA, Lundbeck, Solvay, Abbott, Bial, Merck-Serono, Grunenthal, and Merck Sharp and Dohme. FJP had consultant and speaker fees with Astra Zeneca, Bayer and Boehringer Ingelheim. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

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Research

Original Investigation

Risk of Substantial Intraocular Bleeding With Novel Oral Anticoagulants

Systematic Review and Meta-analysis

Daniel Caldeira, MD; Mário Canastro, MD; Márcio Barra, MSc; Adriana Ferreira, MSc; João Costa, MD, PhD; Fausto J. Pinto, MD, PhD; Joaquim J. Ferreira, MD, PhD

IMPORTANCE In noninferiority trials, novel oral anticoagulants (NOACs), also known as non–vitamin K oral anticoagulants, were at least noninferior to standard care in the prevention of most prothrombotic conditions. However, differences exist in the safety profile of antithrombotic drugs, and little is known about their intraocular bleeding risk.

OBJECTIVE To evaluate the risk of substantial intraocular bleeding associated with NOACs.

DATA SOURCES MEDLINE, Cochrane Library, SciELO collection, and Web of Science databases were searched from inception to November 2014, as well as other systematic reviews and regulatory agencies documentation.

STUDY SELECTION All phase 3 randomized clinical trials (RCTs) comparing NOACs with any other control that reported intraocular bleeding events.

DATA EXTRACTION AND SYNTHESIS Data were extracted independently by 2 of the authors and pooled using random-effects meta-analysis. Heterogeneity was assessed with the I^2 test.

MAIN OUTCOMES AND MEASURES Substantial intraocular bleeding was evaluated with pooled risk ratios (RRs) and 95% CIs.

RESULTS Seventeen RCTs were included. In patients with atrial fibrillation, no difference was identified between NOACs and vitamin K antagonists (RR, 0.84; 95% CI, 0.59-1.19; I^2 = 35%; 5 RCTs), and no increased risk was identified compared with acetylsalicylic acid (RR, 14.96; 95% CI, 0.85-262.00; 1 RCT). In patients with venous thromboembolism, no increased risk of substantial intraocular bleeding compared with sequential treatment with low-molecular-weight heparin and a vitamin K antagonist (RR, 0.67; 95% CI, 0.37-1.20; I^2 = 0%; 5 RCTs) was identified. Regarding patients who underwent orthopedic surgery, the risk was not different between NOACs and low-molecular-weight heparin (RR, 2.13; 95% CI, 0.22-20.50; I^2 = 0%; 5 RCTs).

CONCLUSIONS AND RELEVANCE Randomized data suggest that no differences exist in the risk of substantial intraocular bleeding between NOACs and other antithrombotic drugs. However, the number of events was scarce so that additional studies from larger databases that monitor patients under conditions of ophthalmologic routine clinical practice should be performed to better characterize the safety profile of NOACs.

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The novel oral anticoagulants (NOACs), also called non-vitamin K oral antagonist anticoagulants,[1] are still relatively new agents on the market, and reports describing their risks for patients are still uncommon. The NOACs are safer than existing anticoagulation therapies, significantly reducing intracranial hemorrhage risk compared with vitamin K antagonists (VKAs) and sequential treatment with low-molecular-weight heparin (LMWH) and VKAs.[2] However, safety concerns remain, especially when taking into account that no reversal agent is systematically available. Intraocular hemorrhage is a serious adverse event for patients taking antithrombotic drugs (<1%).[3] Although rare,[4] substantial intraocular hemorrhages can cause severe visual acuity impairment, and in some cases, surgery is needed for complete resolution.[5] Therefore, we aimed to better estimate the risk of substantial intraocular bleeding, a bleeding event defined by default as major bleeding,[6] associated with NOACs through a systematic review and meta-analysis of phase 3 randomized clinical trials (RCTs).

Methods

This systematic review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement as a guideline.[7]

Eligibility Criteria

For this systematic review, we considered published RCTs that evaluated patients treated with NOACs, such as dabigatran etexilate, apixaban, edoxaban, or rivaroxaban, compared with any other active or placebo control. We considered all trials with prothrombotic conditions eligible for anticoagulation treatment, irrespective of patients' baseline disease, drug treatment duration, or follow-up. Only phase 3 RCTs were included to obtain robust data without the bias associated with statistical effects of small, underpowered studies on meta-analysis results.[8-11] Furthermore, we were interested in determining the risk associated with approved NOACs and their commonly used doses.

Information Sources

MEDLINE, Cochrane Library (CENTRAL), SciELO collection, and Web of Science databases (inception to November 8, 2014) were searched to retrieve RCTs evaluating the intraocular bleeding risk of NOACs. The search strategy is outlined in the eMethods in the Supplement. There were no language restrictions.

Reference lists of systematic reviews, as well as the reference list of each included study, were comprehensively searched. Because the conventional search may not detect intraocular bleeds not mentioned in the title or abstract in the electronic record (even though they appear in the full report),[12,13] we sought bleeding data of all published phase 3 RCTs and available public reports of these drugs in the websites of regulatory entities (US Food and Drug Administration, European Medicines Agency, and Australian Therapeutic Goods Administration), similarly to previous work,[14,15] irrespective of the initial search.

Study Selection

After study deduplication, the references obtained in the electronic search were screened independently by 2 authors (D.C. and M.B.) through title and abstract for full-text assessment eligibility. Irrespective of the results of this search, these authors retrieved independently intraocular bleeding estimates of all published and previously identified phase 3 RCTs.

Study characteristics and results were extracted into a standardized form. Included studies were appraised for methodologic bias risk with Cochrane Collaboration's Risk of Bias Tool.[16] Studies were not excluded a priori based on quality reporting assessment.

Outcome Measures

The primary outcome was substantial intraocular bleeding considered by the International Society on Thrombosis and Hemostasis as critical organ bleeding and therefore classified as major bleeding.[6]

Statistical Analysis

We used RevMan software, version 5.3.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), for statistical analysis and to derive a forest plot showing the results of individual studies and pooled analysis. We compared NOACs with controls (active drugs or placebo) through random-effects meta-analysis to estimate pooled risk ratios (RRs) and 95% CIs. The effect measurement estimate chosen was RR because relative measures are more similar across studies with different designs, populations, and lengths of follow-up compared with absolute measures, such as risk difference.[17]

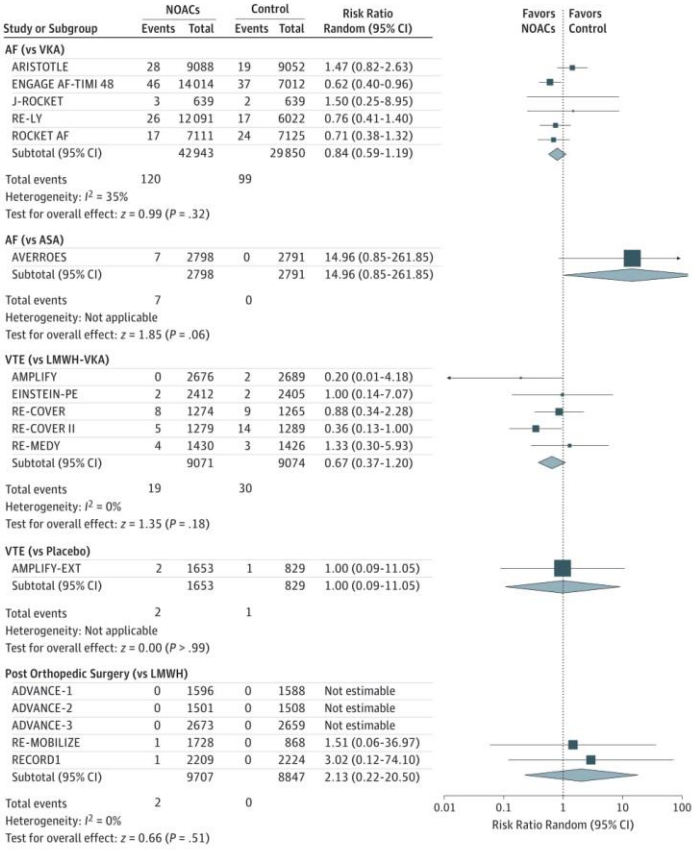
Heterogeneity measured as the percentage of total variation between studies due to heterogeneity was assessed through the I^2 test.[18] We used a Mantel-Haenszel random-effects model irrespective of the existence of substantial heterogeneity between the study results ($I^2 \geq 50\%$) because we pooled results of studies with different designs and patient characteristics. When differences were found ($P < .05$), we planned to determine the number needed to treat and 95% CI, taking into account the control baseline risk.

Pooled analyses were performed according to control groups, which reflect the baseline conditions. Publication bias was assessed through visual inspection of funnel plot asymmetry.

Results

After study selection process (eFigure 1 in the Supplement), 17 RCTs fulfilled the inclusion criteria[19-35]: 6 trials included 78 382 patients with nonvalvular atrial fibrillation (AF) (5 of them were VKA-controlled trials,[19-23] and 1 compared a NOAC [apixaban] with acetylsalicylic acid[24]), 6 RCTs enrolled 20 627 patients with venous thromboembolism (5 trials with LMWH-VKA control[25,27-29,36] and 1 placebo-controlled trial[35]), and 5 trials included 18 554 patients who underwent orthopedic surgery (with LMWH control).[30-34] Further details on included studies are given in the eTable in the Supplement. Overall, the included studies had a low risk of bias (eFigure 2 in the

Figure 1. Forest Plot: Risk Ratios for Intraocular Bleeding With NOACs



ADVANCE indicates Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; AF, atrial fibrillation; AMPLIFY, Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy; AMPLIFY-EXT, Apixaban After the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis With First-Line Therapy-Extended Treatment; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ASA, acetylsalicylic acid; AVERROES, Apixaban vs Acetylsalicylic Acid to Prevent Strokes; EINSTEIN-PE, Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism; ENGAGE AF-TIMI 48, Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48; J-ROCKET, Japanese Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; LMWH, low-molecular-weight heparin; NOACs, novel oral anticoagulants; RECORD1, Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism 1; RE-COVER, Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism; RE-COVER II, Phase III Study Testing Efficacy & Safety of Oral Dabigatran Etexilate vs Warfarin for 6 months Treatment for Acute Symptomatic Venous Thromboembolism; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; RE-MEDY, Secondary Prevention of Venous Thrombo Embolism; RE-MOBILIZE, Oral Thrombin Inhibitor Dabigatran Etexilate vs North American Enoxaparin Regimen for Prevention of Venous Thromboembolism After Knee Arthroplasty; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Supplement). Pooled analysis for the different clinical conditions and controls did not identify an increased risk of substantial intraocular bleeding with NOACs (Figure 1).

Among patients with nonvalvular AF, no difference was identified between NOACs and VKA (RR, 0.84; 95% CI, 0.59-1.19; I^2 = 35%). The incidence of intraocular bleeding events

reported in patients treated with NOACs and VKAs was 0.28% (n = 120/42 943) and 0.33% (n = 99/29 850), respectively.

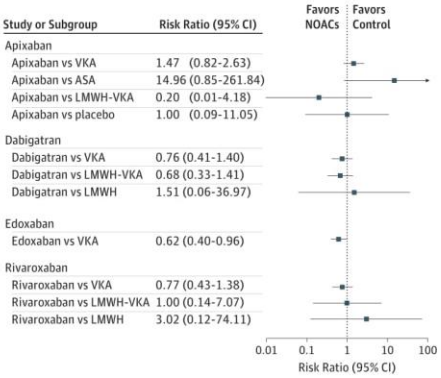
One trial[24] compared a NOAC (apixaban) with acetylsalicylic acid in 5599 patients with nonvalvular AF. The incidence of intraocular bleeding events reported in the apixaban and acetylsalicylic acid groups was 0.25% (n = 7/2798) and 0% (n = 0/2791), respectively (RR, 14.96; 95% CI, 0.85-262.00).

Among patients with venous thromboembolism, no difference was identified between NOACs and sequential LMWH-VKA (RR, 0.67; 95% CI, 0.37-1.20; I^2 = 0%). The incidence of intraocular bleeding events reported in patients treated with NOACs and LMWH-VKA was 0.21% (n = 19/9071) and 0.33% (n = 30/9074), respectively. In the venous thromboembolism extended-treatment placebo-controlled trial,[35] no increased risk of intraocular bleeding was detected.

A total of 18 554 patients undergoing orthopedic surgery were enrolled in 5 RCTs evaluating anticoagulation drugs for thromboprophylaxis. Only 2 of these RCTs reported intraocular bleeding events (one event in patients treated with NOACs and no events in the LMWH control group in each trial), yielding no differences in the risk of intraocular bleeding (RR, 2.13; 95% CI, 0.22-20.50; I^2 = 0%).

Figure 2 shows the risk of intraocular bleeding according to each NOAC and the respective control. With the exception of the comparison between edoxaban and VKAs in nonvalvular AF (RR, 0.62; 95% CI, 0.40-0.96; 1 RCT),[20] all comparisons between individual NOACs and controls were nonsignificant. A funnel plot does not suggest a publication bias toward a specific treatment (eFigure 3 in the Supplement).

Figure 2. Intraocular Bleeding Risk With Each Novel Oral Anticoagulant (NOAC)



ASA indicates acetylsalicylic acid; LMWH, low-molecular-weight heparin; VKA, vitamin K antagonist.

Discussion

Our study highlights the absence of evidence about differences in the risk of substantial intraocular bleeding between NOACs and other antithrombotic drugs, namely, VKAs and LMWH. This information is clinically relevant for ophthalmologists treating patients undergoing intraocular procedures while receiving anticoagulation. The information available comparing NOACs and antiplatelet agents is scarce, and only one trial[24] (Apixaban vs Acetylsalicylic Acid to Prevent Strokes) reported data for this comparison in patients with nonvalvular AF. The differences reported between apixaban and acetylsalicylic acid failed to reach statistical significance. It remains unknown whether this risk could be by chance because the trial was not powered for intraocular bleeding risk estimation. It is also unknown whether baseline characteristics were balanced for intraocular bleeding risk factors.

In the RCTs considered in this systematic review and meta-analysis, only substantial intraocular bleeding (ie, hyphema, vitreous hemorrhage, subretinal hemorrhage, and suprachoroidal hemorrhage) was considered a major bleeding event. This definition respects the criteria established by the International Society on Thrombosis and Hemostasis,[6] excluding minor uncomplicated bleedings, such as subconjunctival hemorrhages.

Patients with neovascular age-related macular degeneration treated with antiplatelet and anticoagulant drugs have an increased risk of intraocular hemorrhage.[37] The clinical relevance of these events relies on the possibility of the development of severe visual acuity impairment.[38] According to a retrospective case-control study, this risk was clearly associated with warfarin treatment and to a lesser extent with antiplatelet drugs,[39] which at least partially overlaps with our results.

In the Randomized Evaluation of Long-Term Anticoagulation Therapy trial,[40] approximately 800 patients treated with dabigatran (and 400 patients treated with VKAs) underwent minor surgery, and approximately one-third of these patients underwent cataract removal. Despite the absence of data specific for eye surgery, the overall estimate for minor surgery did not reveal a significant increased risk of major bleeding (dabigatran etexilate, 110 mg: RR, 1.03; 95% CI, 0.39-2.71; and dabigatran etexilate, 150 mg: RR, 1.75; 95% CI, 0.74-4.14).[40] Despite all this, to the best of our knowledge, no studies with detailed data about NOACs and intraocular bleeding, whether spontaneous or after surgery, have been published. Although cataract surgery appears to be an uneventful and safe surgery to perform in patients undergoing anticoagulation,[41] it is important to clarify the effect of VKAs and NOACs in some types of more invasive ophthalmic operations with greater risks.[42] Unfortunately, whether patients undergoing intraocular surgery are at increased risk of severe hemorrhage with the use of these drugs is not answered by our work. Our data support that existing guidance of other anticoagulations would also be appropriate for NOACs. Published consensus-based guidance specifically for the management of NOACs does not support the withdrawal of anticoagulation in patients undergoing cataract or glaucoma interventions.[4]

In the existing medical literature, there is one case report of intraocular bleeding in an 82-year-old patient who developed a spontaneous choroidal hemorrhage after taking dabigatran for stroke prophylaxis in the context of atrial fibrillation for approximately 1 year.[43]

With the convenience of not having to perform frequent blood draws to monitor the therapeutic international normalized ratio, NOACs are expected to become more popular among patients. The risk of intraocular hemorrhage has to be weighed in each case. Ensuring that an appropriate medication dosage is maintained and paying attention to potential risk factors and hemorrhagic symptoms should be a concern for the treating physician and health care staff.

This analysis is limited by methodologic issues associated with meta-analysis and individual studies. The results of our meta-analysis are based on study-level data and not on individual patient data. Most of these studies were powered for a cardiovascular or a vascular primary outcome and not for a rare specific source of major bleeding as we assess in this review.

Data for our outcomes were not available in some studies, which restrains our review for robust conclusions. In fact, details of intraocular bleeding events were mostly absent from studies. Substantial intraocular bleeding was an uncommon event regardless of the antithrombotic interventions. Our study did not identify intraocular bleeding risk differences, but the wideness of the CIs in some analyses preclude a definite answer.

Pooling data of studies with different designs should also be accounted for as a further methodologic limitation of our study. Nevertheless, it increases the power and external validity of the findings. We also pooled the different NOACs under the assumption of a class effect of these drugs in bleeding events. Despite the pharmacodynamic and pharmacokinetic differences among NOACs,[4] no significant differences were found among NOACs in the meta-analysis.

Conclusions

Overall, NOACs do not increase the risk of substantial intraocular bleeding compared with other anticoagulants (VKAs and/or LMWH). The rate of these serious events was very low (<0.4%) and they were reported in studies that were underpowered for this purpose. Therefore, additional observational studies from larger databases monitoring patients under conditions of ophthalmologic routine clinical practice should be performed to better characterize the safety profile of NOACs.

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Author Contributions: Dr Caldeira had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Caldeira, Costa.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Caldeira, Canastro, Barra, Costa.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Caldeira, Canastro, Costa.
Administrative, technical, or material support: Caldeira, Barra, A. Ferreira, Costa, J. Ferreira.
Study supervision: Caldeira, Costa, Pinto, J. Ferreira.

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Health care delivery, economics and global health

ORIGINAL ARTICLE

Risk of drug-induced liver injury with the new oral anticoagulants: systematic review and meta-analysis

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ABSTRACT

Objective In recent years, safety alerts have been made warning of the risk of serious drug-induced liver injury (DILI) caused by cardiovascular drugs. The new oral anticoagulants (NOACs) have now reached the market. However, safety concerns have been raised about their hepatic safety. Therefore we aimed to evaluate NOAC liver-related safety.

Methods Systematic review and meta-analysis of phase III randomised controlled trials (RCTs). Medline and CENTRAL were searched to September 2013. Reviews and reference lists were also searched. Two reviewers independently searched for studies and retrieved data estimates. Primary outcome was DILI (transaminases elevations >3× upper limit of normal (ULN) with total bilirubin >2× ULN). NOACs were compared against any control group. Random-effects meta-analysis was performed, and pooled estimates were expressed as relative risk (RR) and 95% CI heterogeneity was evaluated with I^2 test.

Results Twenty-nine RCTs evaluating 152 116 patients (mean follow-up of 16 months) were included. All RCTs were rated as having low risk of bias. NOAC were not associated with an increased risk of DILI (RR 0.90, 95% CI 0.72 to 1.13, I^2=0%). Similar results were obtained for individual NOAC (rivaroxaban, apixaban, dabigatran, darexaban, edoxaban) and considering the different control groups (vitamin K antagonists, low molecular weight heparin (LMWH) and placebo). The risk of transaminases elevations (>3×ULN) was lower among NOAC-treated patients, in particular in comparison with LMWH-treated patients (RR 0.71, 95% CI 0.59 to 0.85; I^2=27%)

Conclusions NOACs are not associated with an increased risk of DILI. The unexpected 'protective' effect of NOAC is probably due to LMWH-associated hepatotoxicity.

INTRODUCTION

Most drugs are metabolised in the liver.[1] Drug-induced liver injury (DILI) includes a broad clinical and pathological spectrum of hepatotoxicity and many genetical and non-genetical patient characteristics have been proposed as risk factors for DILI from medications.[2 3] In recent years, safety alerts have been made warning for the risk of DILI, including life-threatening liver failure, caused by cardiovascular drugs. For example, dronedarone, an antiarrhythmic drug, can cause serious liver injury,[4] and ximelagatran, an oral direct thrombin (IIa) inhibitor, has been withdrawn from the market in 2004 due to the risk of DILI.[5] These safety warnings only emerged with postmarketing experience because hepatic adverse drug reactions due to cardiovascular drugs are relatively uncommon, but potentially serious, and premarketing clinical trials are underpowered to detect differences between treatment arms. These recent high profile cases of serious liver adverse reactions associated with cardiovascular drugs have amplified the need for careful premarketing analysis of DILI risk associated safety.

In the last 5 years, new oral anticoagulants (NOACs), with direct inhibition of factors IIa or Xa, have granted European and US marketing authorisation for the prevention of thrombotic events in high-risk adult patients. The past history of ximelagatran further contributed to a close surveillance and reporting of hepatic adverse events during NOAC clinical trials. In fact, with the exception of dabigatran, NOACs are metabolised by the liver (CYP3A4 involvement) and, according to the public assessment reports of these drugs they all are associated with increases in transaminases and abnormal liver function, with an incidence up to 1 in 100 to 1 in 1000 people.[6–8] Furthermore, the 2013 European guidance for the use of NOAC recommends yearly monitoring of liver function.[9]

In this context, we aimed to better estimate the risk of hepatic adverse drug reactions associated with NOAC by performing a systematic review and meta-analysis of phase III randomised controlled trials (RCTs).

METHODS

Guidelines

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses framework guidelines.[10]

Studies' eligibility criteria

Phase III RCTs comparing NOACs, including direct inhibitors of IIa (dabigatran) or Xa (apixaban, darexaban, edoxaban, or rivaroxaban), against any control group (placebo, no-treatment or standard care, non-pharmacological interventions or any drug). Only phase III RCTs were considered to avoid bias in risk estimation due to statistical effects of rare events and the impact of small size underpowered studies on meta-analysis results.[11–14] Furthermore, we were interested in determining the risk associated with the approved and commonly used doses of the NOAC. All RCTs were considered for inclusion irrespective of patients' disease, comorbidities, background therapy, NOAC treatment

duration or follow-up. Only trials reporting hepatic data as a prespecified outcome were included to avoid selective reporting. Trials had to provide laboratory data for transaminases and bilirubin.

Primary outcome was DILI, defined as increases in serum levels of transaminases above three times the upper limit of normal (ULN) and total bilirubin above two times the ULN. According to Hy's law, the outcome defined above is the most specific predictor of potential severe hepatotoxicity.[15] Secondary outcomes were incidence of transaminases elevation >3× ULN, and incidence of bilirubin elevation >2× ULN.

Search method

Investigators retrieved potential eligible studies through an electronic search in Medline and Cochrane Library, run in September 2013. Search strategy for Medline (see supplementary online) included free text and Medical Subjects Headings terms without language restrictions. Additionally, we checked the references of systematic reviews and meta-analyses that evaluated NOAC, as well as the reference list of each included study. When data for pretended outcomes were not available from published articles, we looked at the available public reports of these drugs at the European Medicine Agency and Food and Drug Administration.

Data extraction, evaluation and synthesis

Titles and abstract of obtained records were screened independently by two authors. Doubts and disagreements were solved by consensus. Selected studies were assessed in full text in order to determine the appropriateness for inclusion in the systematic review. Study characteristics and results were extracted independently into a standardised form.

Appraisal of methodological bias was done according to the Cochrane Collaboration's tool for assessing risk of bias.[16] Studies were not excluded a priori based on quality reporting assessment.

Statistical analysis

Results for primary and secondary outcomes were treated as dichotomous data. Risk Ratio (RR) and 95% CI were used to estimate pooled results from studies because relative measurements, such as RR, are more similar across studies with different designs, populations and lengths of follow-up than absolute measurements of treatment effect.[17]

Review Manager V.5.2.6 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) was used to obtain the estimates of individual studies, pooled analysis and to retrieve the forest plots. Heterogeneity was assessed with the I^2 test, which measures the percentage of total variation attributed to interstudy heterogeneity rather than random.[18] The inverse of variance method with random effects model was used by default independently of the existence ($I^2 \geq 50\%$) or not of substantial heterogeneity between studies' results. In case the event rates were <1% in overall NOAC and control groups, we determined the OR of primary outcome through Peto's method, because under these circumstances of relatively rare events the Peto's ORs are a less biased measure.[19]

For outcome analysis, in case the study provided data for both transaminases values, we considered for statistical analysis the results of alanine transaminase due to its higher liver specificity in comparison with aspartate transaminase.[20] Outcome data was analysed according to prespecified subgroups defined by the individual NOAC and type of control group. Differences between subgroups were assessed based on random effects model due to the lower risk of false-positive results.[21]

Publication bias was assessed through visual inspection of funnel plot asymmetry and with Egger's and Peters' regression tests.[22 23]

RESULTS

Results of the search and description of the studies

Figure 1 shows the flow chart of studies' selection and the reasons for studies' exclusion. We were able to include 29 studies enrolling 152 116 patients, 83 513 of them treated with NOACs.[24–50] The NOACs evaluated were apixaban (8 RTCs; 50 259 patients),[24–31] dabigatran (8 RCTs; 34 641 patients),[32–38] darexaban (1 RCT; 156 patients),[39] edoxaban (1 RCT; 7743 patients),[40] and rivaroxaban (11 RCTs; 59 317 patients).[41–50] The number of enrolled patients in each trial ranged from 158 to 18 201. Patients' mean age varied between 55 years and 71 years across trials. About 30% (43 130 patients) of the patients had atrial fibrillation. The weighted mean follow-up was 16.4 months (range, 2 weeks to 2 years).

Low-molecular weight heparin (LMWH) was the most common control group as it was included in 41% of the studies.

The main clinical characteristics of the included studies are shown in online supplementary table S1.

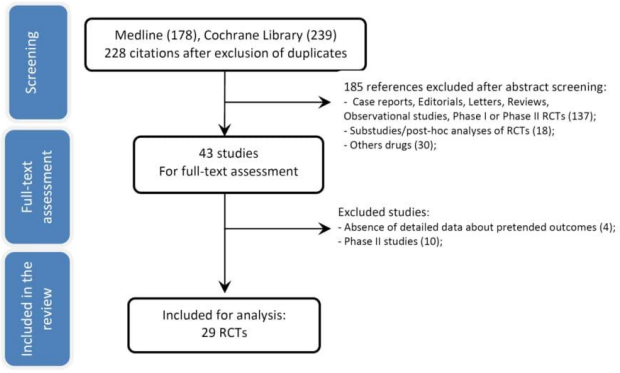

Figure 1 Flow chart of studies selection.

Risk of bias in included studies

Online supplementary figure S1 shows the individual studies' risk of bias appraisal. Overall the risk of bias of the included RCTs was low. The only potential sources of bias identified were the open-label design in four RCTs,[35 39 45 48] and significant data missing from one treatment arm in one RCT.[49] However the lack of blinding in those four RCTs is unlikely to introduce a high risk of bias due to the objective nature of the outcomes.[51]

Risk of DILI

Pooled analysis of 25 studies (4 studies did not provide data for our primary outcome [30 32 33 42]) showed that NOAC does not increase the risk of DILI (transaminases >3× ULN with total bilirubin >2× ULN). The RR was 0.90 (95% CI 0.72 to 1.13). Individually, none of the NOAC increased the risk of DILI and no differences were found between NOAC (p=0.58) in the risk of DILI against control. There was no heterogeneity among studies results (I^2=0%). Figure 2 shows the detailed results for the primary outcome. The funnel plot (see online supplementary figure S2) and Egger's (p=0.61) and Peter's (p=0.58) tests do not suggest small studies' effect or publication bias.

The incidence of DILI was <1% in intervention and control arms (0.22% and 0.24%, respectively). Therefore we also estimated the overall effect with Peto's OR to evaluate the consistency of the results.[19] Pooled Peto's ORs were similar to RR: OR 0.91 (95% CI 0.73 to 1.14) for all NOACs versus controls OR 0.91 (95% CI 0.62 to 1.35) for apixaban, OR 0.68 (95% CI 0.40 to 1.14) for dabigatran, OR 4.42 (95% CI 0.07 to 288) for darexaban, OR 1.94 (95% CI 0.53 to 7.18) for edoxaban and OR 0.97 (95% CI 0.69 to 1.35) for rivaroxaban.

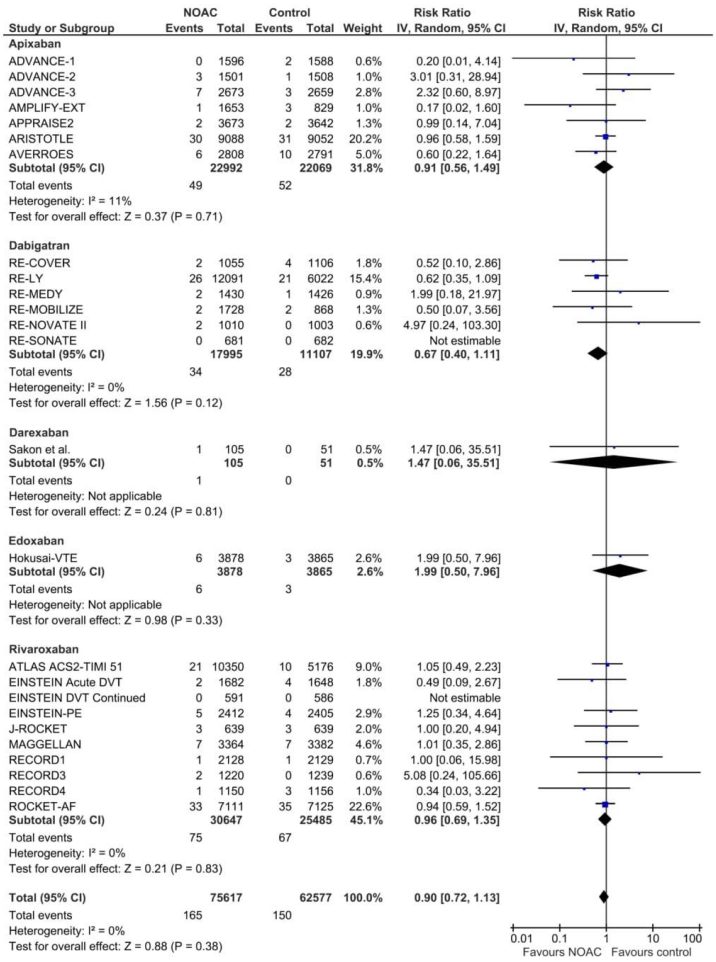

Figure 2 Risk of drug-induced liver injury (elevation of transaminases >3× upper limit of normal (ULN) and of total bilirubin>2× ULN).

Table 1 Risk of DILI (transaminases elevation >3× ULN and bilirubin elevation >2× ULN) according to control group

	Control Group								
	VKA (including LMWH bridging)			LMWH			Placebo/non-pharmacological control		
	RCTs	RR (95% CI)	I^2	RCTs	RR (95% CI)	I^2	RCTs	RR (95% CI)	I^2
Pooled	9	0.88 (0.67 to 1.15)	0%	9	1.20 (0.64 to 2.24)	0%	6	0.91 (0.47 to 1.75)	0%

DILI, drug-induced liver injury; LMWH, low molecular weight heparin; RCTs, randomised controlled trials; RR, risk ratio; ULN, upper limit of normal; VKA, Vitamin K antagonists.

Table 1 shows the risk of DILI associated with NOAC in comparison with the different control groups. As a group, NOAC did not show an increased risk of DILI independently of the control group (Vitamin K antagonists, LMWH and placebo or non-pharmacological treatment). Similar results were obtained for each individual NOAC drug.

Secondary outcomes

Interestingly, NOACs were less likely than controls to have transaminase elevations >3× ULN (RR 0.79; 95% CI 0.70 to 0.90) (figure 3). Low to moderate heterogeneity (I^2=43%) was found between studies. This 'protective' effect was apparently higher among Low Molecular Weight Heparin

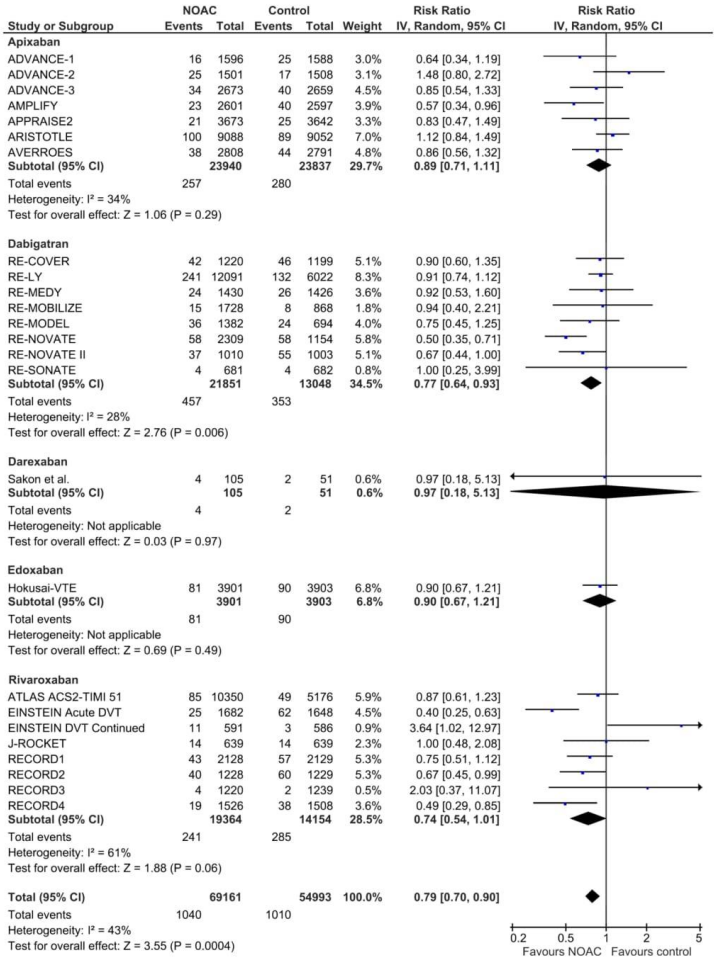

Figure 3 Risk of transaminase elevations >3× upper limit of normal (ULN).

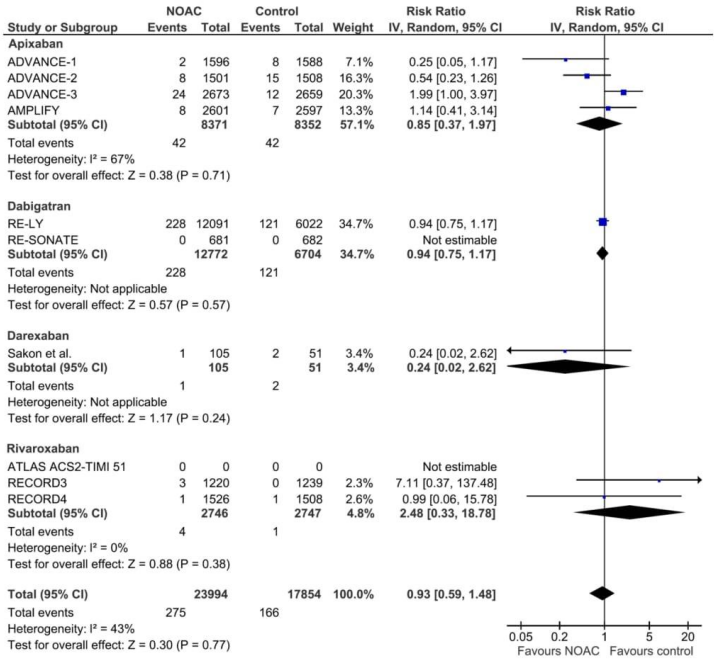

Figure 4 Risk of total bilirubin elevations >2× upper limit of normal (ULN).

(LMWH)-controlled studies. Therefore, we performed an exploratory analysis according to the control group of the trials.

Pooled results from LMWH-controlled trials showed a 29% risk reduction (RR 0.71; 95% CI 0.59 to 0.85) of transaminase elevations among NOAC treated patients in comparison with LWMH, with low to moderate heterogeneity (I^2=27%).

Pooled results from other trials showed non-significant reductions in the risk of transaminase elevation. In the case of Vitamin K antagonists-controlled trials, there was a non-significant 19% risk reduction (RR 0.81; 95% CI 0.64 to 1.02) with moderate to high heterogeneity (I^2=65%).

There were no differences between NOACs and controls in the risk of bilirubin elevations >2× ULN (RR 0.93; 95% CI 0.59 to 1.48; I^2=43%) (figure 4).

DISCUSSION

The main findings of this systematic review are that NOACs are not associated with an increased risk of DILI, based on pooled estimates from large RCTs. Globally, DILI is an uncommon event from a population perspective with an annual incidence rate of 1–2 events *per* 1000 patients.[52] Due to the potential severity of this adverse event it is important to estimate the risk of DILI in the most precise way possible and as soon as possible during the early phase of drug development and before massive postmarketing use. Meta-analysis increases the power to detect group differences. In the case of NOAC, the present meta-analysis included data from about 150 000 patients, more than half exposed to NOAC treatment during a mean duration of 16 months.

Ximelagatran was the anticoagulant that prompted the attention of pharmacovigilance among NOAC studies with respect to hepatic events. It was withdrawn from the market in 2004. The hepatic risk profile of this drug was not noticed in short-term studies (ie, less than 1 month of follow-up). In long-term trials, the increase in serum levels of alanine transaminase (>3× ULN) was sevenfold higher with ximelagatran compared with warfarin. The elevation of transaminases occurred within 6 months after drug initiation, usually after the 1st month of treatment with peak levels of transaminases occurring in the 2nd or 3rd month of treatment.[53]

Our results showed that NOAC in general, and dabigatran in particular (which is not metabolised in the liver), are less likely to increase transaminases than controls, including other commonly used drugs. This finding was unexpected. Interestingly, this putative 'protective' effect of NOAC was more evident in studies which had as control group LMWH. Therefore, one can hypothesise that these results are not due to a true 'protective' effect of NOAC, but rather due to LMWH-associated hepatotoxicity. In fact, hepatotoxicity has been reported to occur in up to 5–10% of LMWH-treated patients.[54] Despite all this, it is unlikely that these results have clinical significance and, therefore, no claims can be made to change the current clinical practice based on these results. Furthermore, there were no differences between NOAC and LMWH regarding the primary outcome, which is a more sensitive measurement of DILI risk.

It is important to stress that the results presented here do not apply to patients with active liver disease because these patients were excluded from the trials. In order to evaluate DILI we

used a simpler and conservative definition of Hy's law, which does not exclude patients with significant cholestasis. So, despite all, there are no signs or trends that the studied drugs increase the risk of DILI. Postmarketing surveillance studies are required to ensure that the results obtained in the meta-analysis of RCTs overlap with those from real-world data.

Limitations

This review includes a meta-analysis of pooled data from phase III RCTs and not from individual patients, which is a potential source of bias in this type of analysis.

Included studies were powered for their cardiovascular primary outcome and not to detect differences with respect to hepatic safety. Data presented here were derived from secondary safety outcomes of included trials and were of very low frequency. Furthermore the data presented here can be biased by the rate of drug discontinuation and losses to follow-up. Therefore, results should be interpreted cautiously.

Heterogeneity of clinical characteristics and interventions/controls across the various studies should also be considered despite the consistency of the results and the absence of significant heterogeneity.

We pooled and interpreted the data of NOAC, which is a group of anticoagulant drugs composed of oral direct thrombin and Xa inhibitors. Nevertheless, it should be further acknowledged that most of the safety data and conclusions presented here were retrieved from trials evaluating apixaban, dabigatran and rivaroxaban in their commonly used doses.

At the outcome level, the data were mainly based on laboratory results. To be more accurate, other causes of hepatic injury and cholestasis should also be evaluated, but data were scarce about these outcomes.

CONCLUSIONS

NOACs such as apixaban, dabigatran, darexaban, edoxaban or rivaroxaban, do not increase the risk of DILI.

Key messages

What is already known about this subject?
The past safety hepatotoxicity history of ximelagatran, an oral anticoagulant, has called the attention of the scientific community to the need of detecting at an early phase of clinical development the possible increased incidence of drug-induced liver injury (DILI) among new oral anticoagulants (NOACs). Although relatively uncommon, DILI can be life-threatening and its potential increased risk with new drugs should be identified as soon as possible and as accurately as possible. Recently, NOACs have reached the market and others are waiting for market approval. The risk of DILI associated with these new drugs is unknown.

How might this impact on clinical practice?
International guidelines recommend the performance of annual liver function tests in patients treated with the NOACs. The estimate of the hepatotoxicity risk associated with NOAC will allow physicians and patients to make more informed therapeutic decisions.

What does this study add?
NOACs such as apixaban, dabigatran, darexaban, edoxaban and rivaroxaban, do not increase the risk of DILI.

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ORIGINAL REPORT

Risk of renal failure with the non-vitamin K antagonist oral anticoagulants: systematic review and meta-analysis

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ABSTRACT

Purpose Vitamin K antagonists (VKA)-related nephropathy is a novel entity characterized by acute kidney injury related to International Normalized Ratio supratherapeutic levels. Non-vitamin K antagonists oral anticoagulants (NOACs) have a predictable dose-response relationship and an improved safety profile. We hypothesized that these drugs do not have an increased risk of incident renal failure, which may be detrimental for the use of NOACs.

Methods Systematic review and meta-analysis of phase III randomized controlled trials (RCTs). Trials were searched through Medline, Cochrane Library and public assessment reports in August 2014. Primary outcome was renal failure. NOACs were evaluated against any comparator. Random-effects meta-analysis was performed by default, and pooled estimates were expressed as Risk Ratio (RR) and 95%CI. Heterogeneity was evaluated with I^2 test.

Results Ten RCTs fulfilled inclusion criteria (one apixaban RCT, three dabigatran RCTs, and six rivaroxaban RCTs), enrolling 75 100 patients. Overall NOACs did not increase the risk of renal failure with an RR 0.96, 95%CI 0.88–1.05 compared with VKA or Low-molecular weight heparin (LMWH), without significant statistical heterogeneity ($I^2 = 3.5\%$). Compared with VKA, NOACs did not increase the risk of renal failure (RR 0.96, 95%CI 0.87–1.07; $I^2 = 17.8\%$; six RCTs). Rivaroxaban did not show differences in the incidence of renal failure compared with LMWH (RR 1.20, 95%CI 0.37–3.94; four trials), but there was an increased risk of creatinine elevation RR 1.25, 95%CI 1.08–1.45; $I^2 = 0\%$.

Conclusions NOACs had a similar risk of renal failure compared with VKA/LMWH in phase III RCTs. Post-marketing surveillance should be warranted. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—renal failure; anticoagulants; meta-analysis; anti-IIa; anti-Xa; pharmacoepidemiology

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INTRODUCTION

Non-vitamin K antagonist oral anticoagulants (NOACs), with direct inhibition of factors IIa or Xa, have been approved for the prevention of thromboembolic events in patients undergoing hip or knee surgery (venous thromboembolism) or those with atrial fibrillation (cardioembolic stroke or systemic embolism). NOACs were also approved for the treatment of venous thromboembolism.

In contrast with vitamin K antagonists (VKA), NOACs have a predictable dose-response without the need of frequent dose adjustments and exempting any control of the anticoagulation status. Overall NOACs also have a faster onset action and decreased risk of major bleeding, particularly intracranial hemorrhage.[1]

All NOACs (with different extensions) are somehow excreted by the kidneys, meaning that in patients with severe renal dysfunction, the concentration of anticoagulant and its effects increase. Safety in this setting is not assured as pivotal clinical studies did not include patients with estimated glomerular filtration rate <25 mL/min. Furthermore, the safety profile of NOACs should be further evaluated.

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The warfarin-related nephropathy was recently described as a new adverse event related to anticoagulant treatment.[2] This entity is characterized by acute kidney injury with supratherapeutic international normalized ratio (INR) values with or without clinically overt hematuria.[2] This novel entity is not fully characterized, but recent studies showed that it was associated to a worse vital prognosis.[2] Different from VKAs, NOACs have a predictable dose-response relationship, and thus, we hypothesized that these drugs do not have an increased risk of incident renal failure. To further evaluate it, we performed a systematic review and meta-analysis of RCTs.

METHODS

Guidelines

Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were used.[3]

Studies' eligibility criteria

We included phase III randomized controlled trials (RCTs) comparing NOACs, against any control group, irrespective of baseline disease. Only phase III RCTs were considered as we were interested in estimating the risk associated with the approved doses of NOACs. By focusing in phase III trials, we avoid the impact of small sized and underpowered studies on meta-analysis results.[4–6]

We considered all trials with prothrombotic conditions eligible for anticoagulation treatment (such as atrial fibrillation (AF), venous thromboembolism (VTE), or patients undergoing hip or knee arthroplasty), irrespective of patients' baseline disease, comorbidities, background therapy, NOAC treatment duration, or follow-up. Trials had to provide data about renal dysfunction or laboratory markers of kidney function.

Primary outcome was that renal failure reported by investigators as an adverse event (or serious adverse event) or an increase of creatinine or blood urea nitrogen deemed to be significant by investigators.

Search method

Investigators retrieved potential eligible studies through an electronic search in Medline and Cochrane Library. Search strategy for Medline is detailed in Supplementary online and it was performed without language restrictions in August 2014. Additionally, we checked the references of systematic reviews and meta-analyses that evaluated NOACs, as well as the reference list of each included study. As the conventional search may not detect adverse effects not mentioned in the title or abstract of the study in the electronic record (even though they appear in the full report),[7,8] we sought for adverse events data of all published phase III RCTs and available public reports of these drugs in the web sites of regulatory entities (US Food and Drug Administration, European Medicines Agency, and Australian Therapeutic Goods Administration), similarly to previous work,[9,10] irrespective of the initial search.

Data extraction, evaluation, and synthesis

Titles and abstracts of obtained records were screened independently by two authors. Doubts and disagreements were solved by consensus. Selected studies were assessed in full text in order to determine the appropriateness for inclusion in the systematic review. Study characteristics and results were extracted independently into a standardized form.

Appraisal of methodological bias was done according to the Cochrane Collaboration's tool for assessing the risk of bias.[11] Studies were not excluded *a priori* based on quality reporting assessment.

Statistical analysis

Results for renal failure were treated as dichotomous data. Risk Ratio (RR) and 95% confidence interval (95%CI) were used to estimate pooled results from studies. Relative measurements, such as RR, were preferred because they are more similar across studies with different designs, populations, and lengths of follow-up than absolute risk measurements of treatment effect.[12]

Stata® Statistical Software Package version 12.0 (StataCorp LP, College Station, Texas, USA) was used to obtain the estimates of individual studies, pooled analysis, and forest plots. Heterogeneity was assessed with the I^2 test, which measures the percentage of total variation attributed to inter-study heterogeneity rather than random.[13] The random-effects model was used in the meta-analysis independently of the degree of heterogeneity.

Publication bias was assessed through funnel plot visual inspection and with Egger's and Peters' regression tests.[14,15]

Subgroup evaluations according to comparator group and specific NOAC were performed. We expected different definitions for incident renal failure as an adverse event; therefore a pooled analysis according to outcome definition was planned.

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RESULTS

Results of the search, description and risk of bias of included studies

Evaluation of potential eligible studies retrieved 10 phase III RCTs for inclusion in the systematic review: one study with apixaban,[16] three with dabigatran,[17–19] and six with rivaroxaban.[20–25] Most of the data were retrieved from public assessment reports. Flowchart of studies selection is detailed in Supplementary Figure 1.

These trials enrolled overall 75 100 patients. The mean age of patients included in RCT ranged from 55 to 73 years. Four trials enrolled patients with AF, two RCTs with VTE-patients, and four trials with patients that underwent orthopedic surgery. We included six VKA-controlled RCTs[16–21] and four LMWH-controlled RCTs.[22–25] In VKA-controlled trials, the INR target was 2.0–3.0, with exception in J-ROCKET where patients with ≥70 years had an INR target of 1.6–2.6.[20] Follow-up varied between 1 month (post-orthopedic surgery thromboprophylaxis RCTs) and 2 years. No trial include patients with estimated glomerular filtration rate <25 mL/min.

Renal failure as increase of serum creatinine was the outcome sought in three studies,[16,18,19] treatment-emergent adverse event (TE AE) for one study,[20] and treatment-emergent serious adverse events (TE SAE) for two studies.[17,21] For RECORD (1–4) studies,[22–25] a series of trials evaluating rivaroxaban versus low-molecular weight heparin (LMWH) in patients undergoing orthopedic surgery, two outcomes of interest were available: overall TE SAE acute renal failure (for all the four trials together) and increase of serum creatinine (separately for RECORD 1–2,[22,23] and RECORD 3–4[24,25]). For the purposes of main analysis, we took the TE SAE acute renal failure of the four trials. For secondary analyses, we also included data from reported increase of creatinine.

Table 1 shows the characteristics of included studies.

Concerning bias risk of individual studies, RE-LY had high risk for performance bias because of the open-label design.[17] All studies were at high risk of potential reporting bias because the retrieved outcomes were not prespecified and renal failure was not systematically assessed.

The qualitative risk of bias assessment is shown in Supplementary Figure 2.

Risk of renal failure

We had data available from 10 RCTs with 75 100 patients for primary analysis (40 507 treated with NOACs). Overall NOACs did not increase nor decrease the risk of renal failure (RR 0.96, 95%CI 0.88–1.05; $I^2 = 3.5\%$) (Figure 1).

Compared with VKA (warfarin), NOACs estimate overlap with those from primary analysis showing RR 0.96 (95%CI 0.87–1.07; $I^2 = 17.8\%$). The data from four RCTs comparing rivaroxaban with LMWH (RECORD trials) did not show differences in the incidence of renal failure between interventions (RR 1.20, 95%CI 0.37–3.94).

Pooled analyses across all included baseline conditions overlapped the results of the main analysis (Supplementary Figure 3)

Results for individual NOACs are detailed in Figure 2: Apixaban did not increase the risk of renal failure (RR 0.97, 95%CI 0.88–1.07; one trial); Rivaroxaban did not show a significant increase of renal failure but there was a trend for increased risk (RR 1.43, 95%CI 0.63–3.24; six trials) and significant statistical heterogeneity was observed ($I^2 = 66.7\%$); and dabigatran did not show increased risk of renal failure (RR 0.92, 95%CI 0.73–1.16; $I^2 = 0\%$, three trials).

Analysis according to renal failure definition was performed. J-ROCKET that was the only study reporting TE AE renal impairment and significant increased risk of this adverse event was noticed in this trial (Figure 3). The remaining trials with other renal failure definitions did not show an increased risk of renal failure with NOACs (Figure 3).

The use of other outcomes for RECORD trials (RECORD 1–2: increase of serum creatinine; and RECORD 3–4 twofold upper limit of normal of serum creatinine) was remarkable for an increase of renal failure risk in rivaroxaban arm versus LMWH (RR 1.25, 95%CI 1.08–1.45; $I^2 = 0\%$), without increasing overall NOACs renal failure risk (RR 1.04, 95%CI 0.90–1.19; $I^2 = 55.7\%$) (Figure 4). Overall rivaroxaban's renal failure risk was still not significant (RR 1.43, 95%CI 0.63–3.24; $I^2 = 66.7\%$).

An adequate visual evaluation of the funnel plot requires at least 10 estimates in the graph, nevertheless, publication bias risk was not significantly increased by plot visualization (Supplementary Figure 4) or through Peters test ($p = 0.17$) and Egger test ($p = 0.31$).

DISCUSSION

The main finding of this systematic review was that NOACs risk of renal failure was similar to other anticoagulant drugs such VKA or LMWH. Despite some limitations inherent to the method (meta-analysis) and data included (heterogeneous definitions of the

Table 1. Main characteristics of included studies

	Trial	Total number of patients (NOACs vs. comparator)	NOAC versus comparator	Mean/median age (SD/IQR)(years)	Follow-up	Outcome retrieved
Atrial fibrillation	**ARISTOTLE**	23 729 (11 843 vs. 11 896)	Apixaban 5 mg bid* versus VKA INR 2.0–3.0 TTR 62.2%	70 (63–76)	1.8 years	Significant elevation of serum creatinine[¥]
	J-ROCKET	1298 (639 vs. 639)	Rivaroxaban 15 mg od[#] vs. VKA INR 2.0–3.0 and ≥70 years 1.6–2.6 TTR 65%	71.1 (range 34–90)	1.3 years	TE AE: renal impairment
	RE-LY	18 040 (12 042 vs. 5998)	Dabigatran Etexilate 110 mg bid and 150 mg bid vs. VKA INR 2.0–3.0 TTR 64%	71.5 (8.7)	2.0 years	TE SAE: acute renal failure
	ROCKET AF	14 236 (7111 vs. 7125)	Rivaroxaban 20 mg od[§] vs. VKA INR 2.0–3.0 TTR 55%	73 (65–78)	1.9 years	TE SAE: acute renal failure
VTE	**RE-MEDY**	2856 (1430 vs. 1426)	Dabigatran Etexilate 150 mg bid vs. VKA INR 2.0–3.0 TTR 65.3%	55 (15)	6 months	Elevation of serum creatinine[¥]
	RE-COVER II	2568 (1279 vs. 1289)	Dabigatran Etexilate 150 mg bid vs. VKA INR 2.0–3.0 TTR 57%	56	6 months	Elevation of serum creatinine[¥]
Prevention of VTE in orthopedic surgery	**RECORD 1**	4433 (2209 vs. 2224)	Rivaroxaban 10 mg od vs Enoxaparin 40 mg od	63	30 to 35 days	Treatment-emergent adverse event: acute renal failure; elevation of serum creatinine[¥]
	RECORD 2	2509 (1252 vs. 1257)	Rivaroxaban 10 mg od vs Enoxaparin 40 mg od	61.5	30 to 35 days	Treatment-emergent adverse event: acute renal failure; elevation of serum creatinine[¥]
	RECORD 3	2531 (1254 vs. 1277)	Rivaroxaban 10 mg od vs Enoxaparin 40 mg od	67.6	30 to 35 days	Treatment-emergent adverse event: acute renal failure; creatinine 2x ULN
	RECORD 4	3148 (1584 vs. 1564)	Rivaroxaban 10 mg od vs Enoxaparin 30 mg bid	64.5	30 to 35 days	Treatment-emergent adverse event: acute renal failure; creatinine 2x ULN

The sample sizes of studies do not match with those of the meta-analysis, because the latter correspond mostly to the safety populations.
bid: twice daily; INR: international normalized ratio; IQR: interquartile range; NOAC: non-vitamin K oral anticoagulant; od: once daily; SD: standard deviation; TTR: time in therapeutic range; ULN: upper limit of normal.
*Apixaban 2.5 mg if two or more of the following: >80 years, <60 Kg or serum creatinine > 1.5 mg/dL.
[#]Rivaroxaban 10 mg od if creatinine clearance 30–49 mL/min.
[§]Rivaroxaban 15 mg od if creatinine clearance 30–49 mL/min.
[¥]Degree of elevation not defined.

outcome), the results are robust as they were derived from 10 RCTs enrolling more than 75 000 patients.

The recognition of warfarin-related nephropathy as a relevant adverse event related to anticoagulants prompted our systematic review. The microscopic landmark of this entity is the tubular obstruction by red blood cell casts in patients treated with VKA with supratherapeutic INR levels.[26] Differently from these drugs, NOACs have a predictable dose-response effect and a lower risk for major bleeding events (a cause of acute renal failure) in atrial fibrillation,[27] thus, it was not surprising that these drugs did not show an increased risk for renal failure compared with VKA. Conversely, Xa inhibitors such as rivaroxaban have shown increased risk of major bleeding against LMWH for the thromboprophylaxis in patients having total hip or knee replacement.[28] This may explain the increased risk of renal failure (defined as the pooled results of creatinine increase and creatinine 2x upper limit of normal (ULN)) in the secondary analysis associated to rivaroxaban in LMWH-controlled trials. However, when we used renal failure SAE (reflecting the seriousness of the adverse event according to the investigator) as occurred in the primary analysis, rivaroxaban's risk was similar to LMWH.

All NOACs have a renal excretion (more extensively with dabigatran and less extensively with apixaban) and renal impairment would potentiate the bleeding risk through drug metabolite retention. This supported the exclusion criterion regarding

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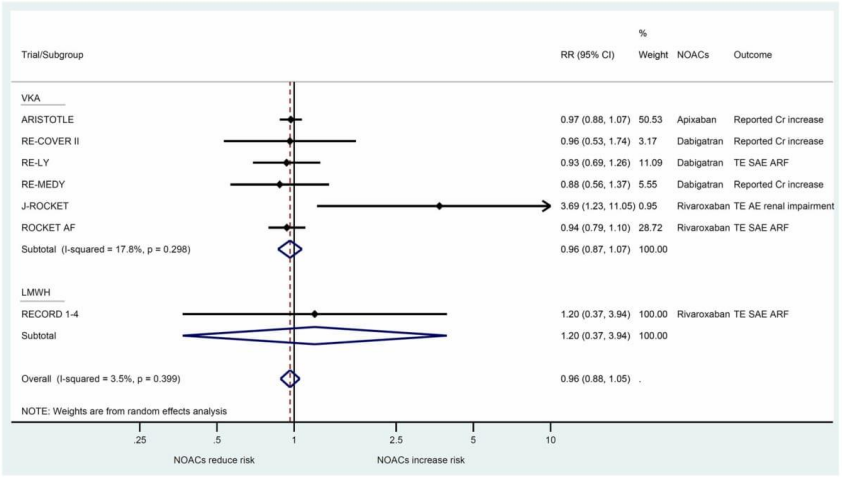

Figure 1. Meta-analysis of non-vitamin K antagonists oral anticoagulants' (NOACs) renal failure according to control group. CI, confidence interval; TE AE, treatment-emergent adverse event; TE SAE, treatment-emergent serious adverse events; VKA, vitamin K antagonists; LMWH, low-molecular weight heparin

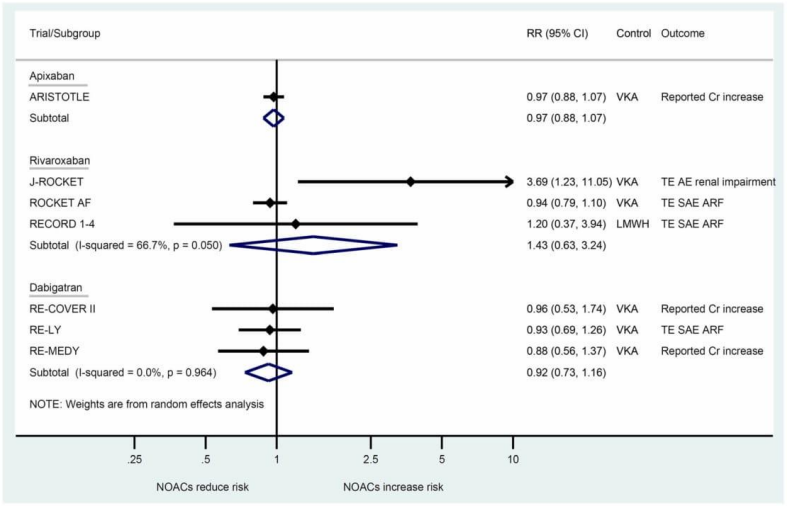

Figure 2. Meta-analysis of renal failure according to individual non-vitamin K antagonists oral anticoagulants (NOACs). CI, confidence interval; VKA, vitamin K antagonists; LMWH, low-molecular weight heparin

patients with severe renal impairment (creatinine clearance < 25 or 30 mL/min) in the pivotal trials. Considering that such degree of kidney dysfunction would make the patients theoretically ineligible for NOACs treatment, our meta-analysis was essential to ensure the renal safety of NOACs.

Besides the drug-treatment implications, renal failure increases the risk of thromboembolic and bleeding

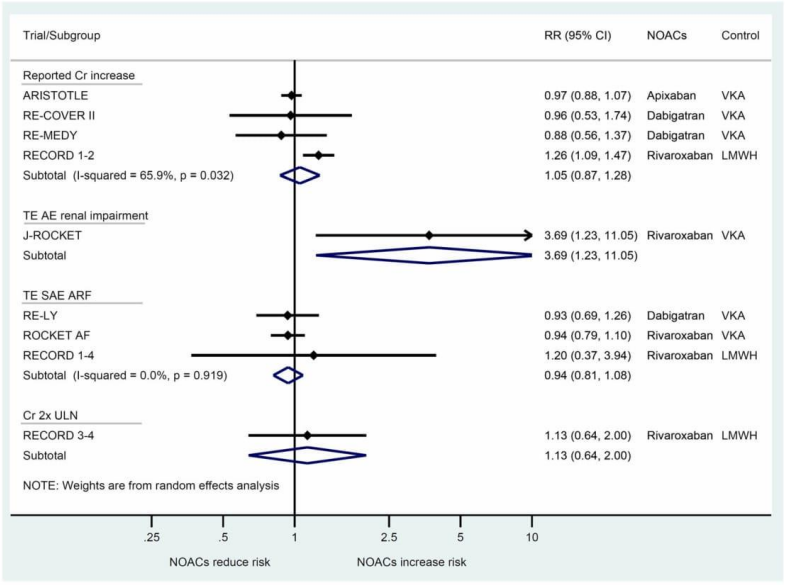

Figure 3. Meta-analysis of renal failure of non-vitamin K antagonists oral anticoagulants (NOACs) according to outcome definition. CI, confidence interval; VKA, vitamin K antagonists; LMWH, low-molecular weight heparin

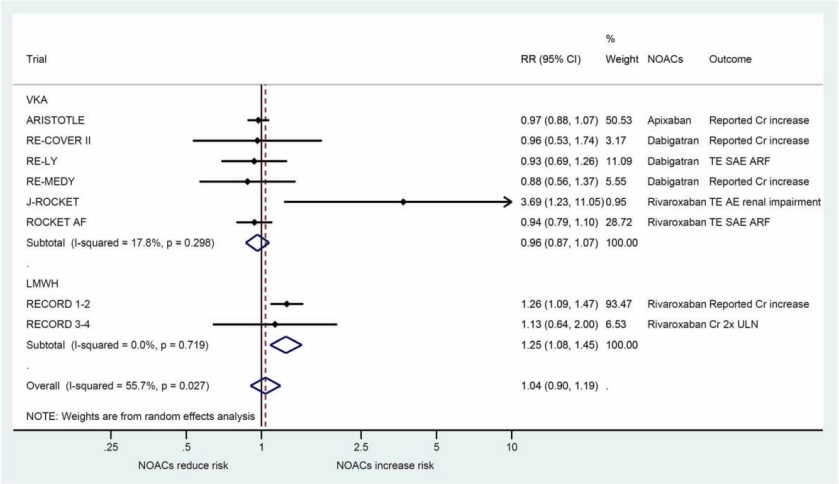

Figure 4. Meta-analysis of renal failure of non-vitamin K antagonists oral anticoagulants (NOACs) according to control group, using alternative data for RECORD trials. CI, confidence interval; TE AE, treatment-emergent adverse event; TE SAE, treatment-emergent serious adverse events; VKA, vitamin K antagonists; LMWH, low-molecular weight heparin

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events in patients with atrial fibrillation,[29–31] which is the most prevalent cause for life-long anticoagulation. Renal dysfunction is considered to be a risk factor for stroke in AF patients,[29,30] but it is not contemplated in the widely disseminated thromboembolic risk stratification tool CHA2DS2-VASc score.[31] As for major bleeding, renal dysfunction is accounted for the HAS-BLED,[32] a recognized tool for bleeding risk stratification in patients with AF.[33]

LIMITATIONS

This review provides robust data but has limitations that should be acknowledged. The data here assessed results from meta-analysis of RCTs and not from individual patient data analysis, thus owing a potential risk bias.

Most of these pivotal studies were powered for cardiovascular primary outcome assessment. One of the most important limitations is related to the nature and aims of included studies that were not designed to detect acute kidney injury (data on renal status was not prespecified and methodically obtained) or to adjudicate its cause. Therefore, at outcome level, the heterogeneity in the definition of outcomes should be noticed as well as the selective reporting bias. Furthermore this systematic review was not able to capture differences the clinical consequences and severity that vary widely, from asymptomatic creatinine rise to a patient requiring haemodialysis. These were the major methodological drawbacks of this systematic review.

J-ROCKET appeared to be an outlier in the analyses. This condition can be related to the outcome definition, small sample size, or due to the selective reporting bias. A sensitivity analysis was further performed excluding J-ROCKET but results overlap the main analysis (data not shown).

We pooled and interpreted the data of NOACs as a group of anticoagulant drugs composed by oral direct thrombin and Xa inhibitors. The low-to-moderate statistical heterogeneity in the main analysis may suggest a drug-class effect, supporting a consistent safety profile, transversal to all considered NOACs.

CONCLUSIONS

Non-vitamin K oral anticoagulants, such as apixaban, dabigatran, and/or rivaroxaban, showed a similar risk of renal failure compared with other anticoagulants in phase III RCTs. Rivaroxaban showed an increased risk of creatinine elevation. 'Real World' post-marketing surveillance should be warranted in order to confirm these data.

CONFLICT OF INTEREST

D. C., N. G., and J. C. do not have any competing interests to disclose. J. J. F. had speaker and consultant fees with GlaxoSmithKline, Novartis, TEVA, Lundbeck, Solvay, Abbott, Bial, Merck-Serono, Grunenthal, and Merck Sharp and Dohme. F. J. P had consultant and speaker fees with Astra Zeneca, Bayer, and Boehringer Ingelheim.

KEY POINTS

- The Warfarin-Related Nephropathy was recently described as a new adverse event related to anticoagulant treatment.
- The use of NOACs in patients with moderate/severe renal dysfunction is not recommended, so worsening of renal function with these drugs would be detrimental of its use.
- In this meta-analysis, NOACs did not show increased risk of renal failure.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

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AUTHOR CONTRIBUTORS

D. C. contributed to the concept and design, data acquisition, data analysis, and interpretation of the data; wrote the first draft of the manuscript; critically revised the manuscript; and gave final approval of the submitted manuscript. J. C. contributed to the data acquisition and data analysis; critically revised the manuscript; and gave final approval of the submitted manuscript. N. G., F. J. P., and J. J. F. contributed to the interpretation of data, critically revised the manuscript, and gave final approval of the submitted manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at publisher's website.

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ORIGINAL ARTICLE

Risk of insomnia with non-vitamin K oral anticoagulants: systematic review and meta-analysis

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Abstract
Purpose Insomnia is an important adverse event of mechanical thromboprophylaxis. This sleep disorder has been reported as one of the commonest adverse events of the new oral anti-Xa anticoagulant darexaban, with similar rates to mechanical thromboprophylaxis in a randomized controlled trial (RCT). However, the perceived effect could have been biased because it was an open-label RCT. Therefore, we aimed to review the incidence of insomnia with non-vitamin K antagonist oral anticoagulants (NOACs).
Methods We performed a systematic review and meta-analysis of Phase III RCTs. Electronic databases MEDLINE and CENTRAL (inception to September 2013) were searched as well as review articles and references of included studies.

We included phase III RCTs which compared NOACs with any other control group. Data were analyzed and pooled to estimate risk ratio (RR) with 95% confidence intervals (95%CI) for insomnia using inverse variance method. Statistical heterogeneity was evaluated with I^2 test.
Results We included seven studies (two apixaban RCTs, two dabigatran RCTs, one darexaban RCTs, and two rivaroxaban RCTs), enrolling a total of 23,023 patients. Overall, NOACs were not associated to an increased risk of insomnia: RR 0.94 (95%CI 0.83–1.08; I^2=0%). In blinded studies (six studies), NOACs also did not show increased risk of insomnia (RR 0.94, 95%CI 0.83–1.08; I^2=0%). Results were similar irrespective of the comparators.
Conclusions NOACs (apixaban, dabigatran, darexaban, rivaroxaban) did not show increased risk of insomnia. Results according to study design (blinded vs. open-label trials) overlap the main analysis.

Keywords Insomnia · Sleep initiation and maintenance disorders · Anticoagulants · Drug-related side effects and adverse reactions

Electronic supplementary material The online version of this article (doi:10.1007/s11325-014-1112-8) contains supplementary material, which is available to authorized users.

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Introduction

Insomnia is common sleep disorder characterized by difficulty to initiate or maintain sleep [1]. This condition can lead to impaired life quality and inability to adequately perform many tasks of daily living activities [2, 3]. Insomnia has been reported as an adverse drug reaction for several drugs. Darexaban, an anti-Xa oral anticoagulant, has shown a high rate of insomnia in a phase III randomized mechanical prophylaxis-controlled trial, although it was not different than the

proportion of insomnia reported in patients with mechanical thrombophylaxis [4]. Insomnia is known to be an important adverse event associated to mechanical thromboprophylaxis [5], and very similar rates of insomnia between darexaban and thromboprophylaxis were not expected. However, since the trial had an open-label design, the perception of adverse events by patients and/or physicians may have been biased. It is known that the lack of blinding is associated with oversized estimates effects of interventions [6]. Furthermore, insomnia-related adverse events may be reported in a subjective manner [7], which is an additional reason to reassure the safety profile of these drugs.

Therefore, to further elucidate the safety profile of the non-vitamin K antagonist oral anticoagulants (NOACs), we aimed to review the risk of insomnia of these drugs by performing a systematic review and meta-analysis of phase III randomized clinical trials.

Methods

Preferred reporting items for systematic reviews and meta-analyses (PRISMA) framework statement was used for reporting data [8].

Studies' eligibility criteria

In this review, we intended to evaluate phase III randomized controlled trials (RCTs) comparing non-vitamin K antagonist oral anticoagulants (NOACs) with any other strategy (placebo, standard care, or other defined antithrombotic drugs). We included all trials that filled the previous criteria, irrespective of studied diseases, comorbidities, treatment duration or studies' follow-up. Other background treatments were not an exclusion criterion. Trials should report the outcome of interest: insomnia. We were not restrictive and we accepted all reports of insomnia, irrespective of its definition (including the judgment of each individual investigator).

Search method

The investigators retrieved potential eligible studies through an electronic search in MEDLINE and Cochrane Library in December 2013. Search strategy for MEDLINE database (in Supplementary online) included free text and medical subject headings (MeSH) terms without language restrictions. Additionally, we verified the references of systematic reviews and meta-analyses that evaluated approved NOACs such as apixaban, dabigatran, and rivaroxaban. Furthermore, the reference list of each included article was also screened.

Data extraction, evaluation, and synthesis

Titles and abstracts of obtained records were screened independently by two authors. Doubts and disagreements were solved by consensus. Selected studies were assessed in full text in order to determine the appropriateness for inclusion in the systematic review. Study characteristics and results were extracted into a standardized form and evaluated independently by two authors.

The following data were comprehensively retrieved from obtained studies: population characteristics/demographics, description of interventions, and the primary outcome of this systematic review (insomnia).

Appraisal of methodological bias risk was done using Cochrane Collaboration's Tool [9]. Risk of bias plots were derived according to the following characteristics of the Tool: randomization method, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, selective reporting, description of withdrawals, and other biases [9]. Studies were not excluded based on reporting quality.

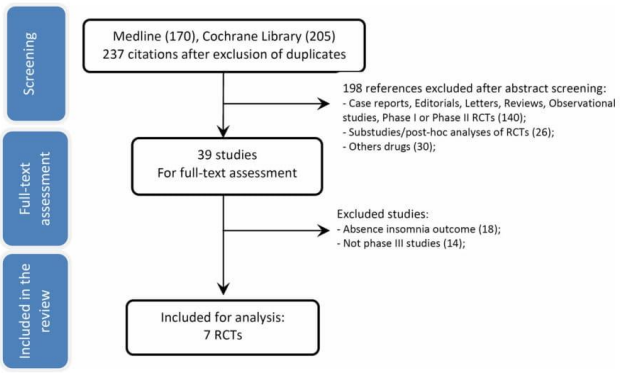

Fig. 1 Flowchart of studies selection

Table 1 Main characteristics of included RCTs

Year	Study acronym	Patients	Mean age	Active group	Control group	Follow-up	Primary outcome
Apixaban							
2009	ADVANCE-1	3195 Patients who underwent total knee replacement	66	1596 Patients with 2.5 mg of apixaban BID	1588 Patients with 30 mg of subcutaneous enoxaparin BID	60 days after anticoagulation period	VTE events and all-cause mortality
2011	APPRAISE-2	7392 Patients with recent ACS	67	3705 Patients apixaban 5 mg BID	3687 Patients placebo	241 days	CV death, myocardial infarction, or ischemic stroke
Dabigatran							
2007	RE-NOVATE	3494 Patients who underwent primary elective unilateral total hip replacement	64	1146 Patients Dabigatran 220 mg OD; 1163 patients Dabigatran 150 mg	1154 Patients enoxaparin 40 mg OD	2 and 3 months after surgery	VTE events and all-cause mortality
2011	RE-NOVATE II	2013 Patients undergoing primary, unilateral, elective total hip arthroplasty	62	1010 Patients dabigatran 220 mg OD	1003 Patients enoxaparin 40 mg OD	3 months	VTE events and all-cause mortality
Darexaban							
2012	Sakon et al.	117 Patients who underwent major abdominal surgery	64	77 Patients darexaban 15 mg BID	40 Patients mechanical thromboprophylaxis	29 days	VTE events at day 12
Rivaroxaban							
2008	RECORD1	4433 Patients who underwent elective total hip arthroplasty	63	2209 Patients rivaroxaban 10 mg OD	2224 patients Enoxaparin 40 mg OD	30 to 35 days	Deep-vein thrombosis, pulmonary embolism and death
2008	RECORD3	2509 Patients who underwent total knee arthroplasty	68	1254 Patients rivaroxaban 10 mg OD	1277 patients enoxaparin 40 mg OD	30 to 35 days	VTE events and death.

BID twice daily, *CV* cardiovascular; *INR* international normalized ratio, *OD* once daily, *VKA* vitamin K antagonists, *VTE* venous thromboembolic events

Statistical analysis

Results for insomnia were treated as dichotomic data. Estimates were reported as risk ratio (RR) with their 95% confidence intervals (95%CI). Relative measures were used to report the interventions' effect because these are more similar across studies with different designs, populations, and lengths of follow-up than absolute effects [10].

Review Manager 5.2.6 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.) was used to obtain the estimates of individual studies, pooled analysis and to retrieve the forest plots. Heterogeneity in the pooled analysis was assessed through the I^2 test, which measures the percentage of total variation attributed inter-study heterogeneity rather than random [11]. For the pooled analysis, we used the inverse variance method with random effects model independently of the existence ($I^2 \geq 50\%$) of substantial heterogeneity between studies' results. We pooled the results of the studies with different control groups and patients' characteristics.

Data were evaluated according to the different NOACs, study design (blinded trials vs. open-label trials) and control groups.

Publication bias was assessed through visual inspection of funnel plot asymmetry and Egger's and Peters' regression tests [12, 13].

Results

Results of the search and description of studies

Database search was performed in MEDLINE and Cochrane Library databases in December 2013.

Figure 1 shows the flowchart of studies' selection with the reasons for studies' exclusion.

Seven phase III RCTs reported the frequency of insomnia as an adverse event [4, 14–19]. Overall, these trials included 23,192 patients, but only 22,867 patients were included for safety analysis. Table 1 details the main characteristics of these studies.

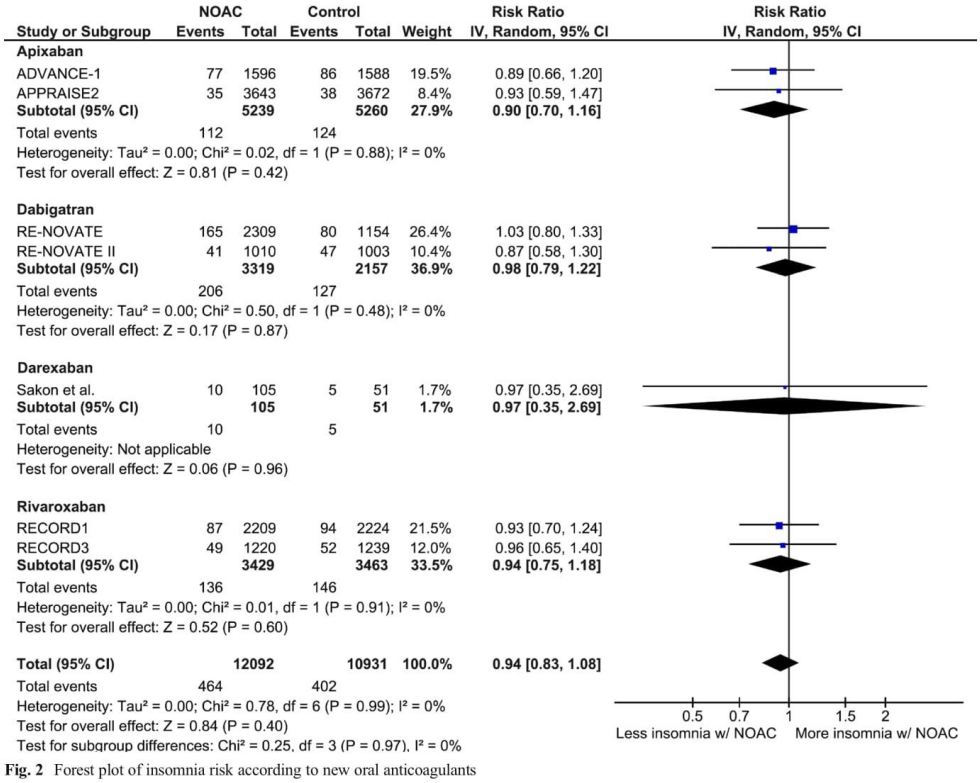

Fig. 2 Forest plot of insomnia risk according to new oral anticoagulants

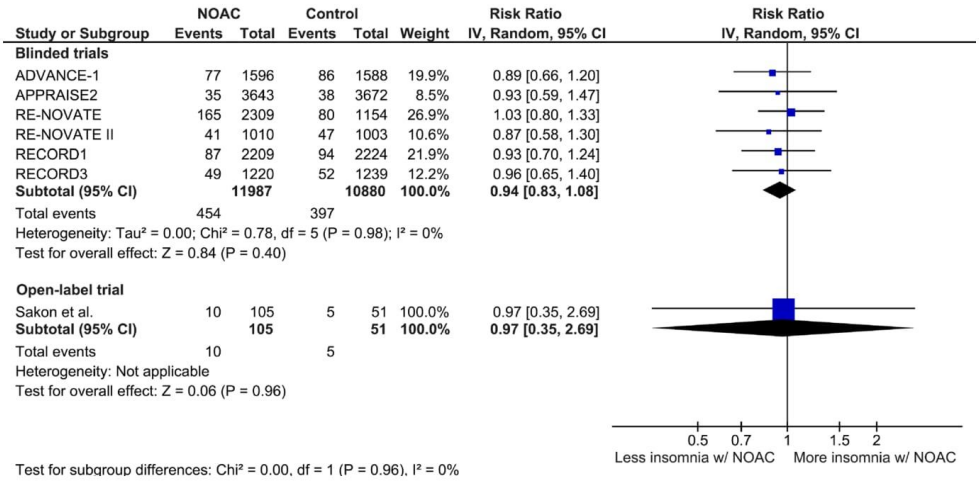

Fig. 3 Risk of insomnia with NOACs according to study design (open label or blinded)

Darexaban was studied in one trial that included patients undergoing major abdominal surgery and randomized to this NOAC or mechanical thromboprophylaxis [4]. There were no differences in insomnia reporting between both interventions.

Apixaban was evaluated in two studies with 10,499 patients [14, 15]. One study compared apixaban with enoxaparin [14] and other with placebo [15]. Individually, none of the studies showed statistical differences regarding insomnia. In the pooled analysis, apixaban did not show increased risk of insomnia with a RR 0.90 (95%CI 0.70–1.16; I^2=0%).

Dabigatran's risk of insomnia was evaluated in two enoxaparin-controlled trials with 5476 patients [16, 17]. No increased risk of insomnia was found with this drug: RR 0.98 (0.79–1.22; I^2=0%).

Rivaroxaban data were also based in two studies with enoxaparin as control [18, 19]. Pooling these data with 6892 patients, the RR was 0.97 (95%CI 0.75–1.18; I^2=0%).

Overall, the meta-analysis including all the previously mentioned studies showed that NOACs did not increase the risk of insomnia, RR 0.94 (95%CI 0.83–1.08; I^2=0%), and no

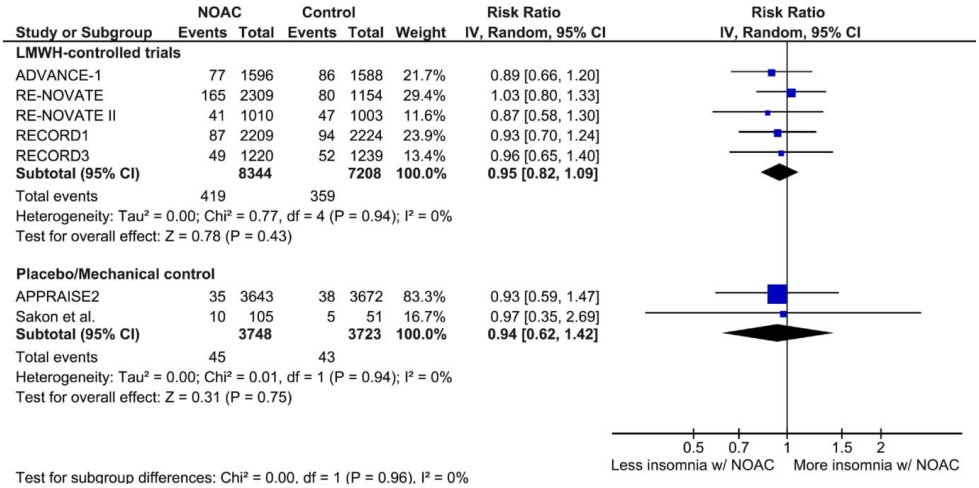

Fig. 4 Risk of insomnia with NOACs according to control group

differences were found between each of these drugs (p=0.97). Figure 2 shows the forest plot of the meta-analysis.

One of the purposes of this review was to evaluate whether the study design (open label vs. blinded studies) had an impact in the risk of insomnia. In blinded studies, NOACs were not associated to increased risk of insomnia (RR 0.94, 95%CI 0.83–1.08; I^2=0%) (Fig. 3).

The type of control did not have impact in the estimates (Fig. 4). NOACs were not also associated to insomnia in low molecular weight heparin (LMWH), mechanical thromboprophylaxis, and placebo-controlled trials (Fig. 4).

Risk of bias

The risk of bias of the included RCTs was globally low (Supplementary Figure 1). Selective reporting was the main source of bias, as insomnia was not a pre-determined outcome and investigators did not actively look for this outcome.

The results of the meta-analysis were not suggestive of publication bias. The small number of included studies hampers the interpretability of the funnel plot (Supplementary Figure 2) [20]. However, both Egger (p=0.32) and Peters (p=0.59) tests were not positive for publication bias.

Discussion

This systematic review did not show increased risk of insomnia with NOACs. This question was driven by the results of a RCT comparing darexaban with mechanical prophylaxis in the prevention of venous thromboembolism in patients undergoing major abdominal surgery [4]. One of the points of interest of this trial was its open-label design, with the reported incidence of insomnia being high despite the absence of differences among the interventions. We would expect that the risk of insomnia with mechanical thromboprophylaxis to be higher compared to darexaban, and we hypothesized that the study design could have influenced the estimates. The results of this meta-analysis showed that NOACs were not associated to insomnia in blinded studies, regardless of the comparators.

Cardiovascular drugs are uncommonly linked to this adverse event, but beta-blockers have been associated to sleep disorders, insomnia included [21, 22]. Regarding antithrombotic drugs, there is no record of increased risk of insomnia of these drugs. This reinforces that the best available evidence did not reveal any increased risk of this adverse event with the approved NOACs. The results of this study were derived from trials with increased risk of selective reporting, and thus post-marketing surveillance studies are warranted in order to ensure that this event does not occur more frequently with NOACs than in the general population.

The reader must acknowledge that this review includes a meta-analysis with data from RCTs and not from individual patients, which is a potential source of bias in this type of analysis. Heterogeneity of clinical characteristics and interventions/controls across the various studies should be considered despite the absence of significant statistical heterogeneity and results' consistency. The already mentioned selective reporting bias is also a limitation of our conclusions.

Conclusions

In this systematic review, we showed that new oral anticoagulants, either individually or globally, did not increase the risk of insomnia based on randomized controlled trial data.

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Conflict of interest DC, MB, DdA, ATS, and JC do not have any competing interests to disclose. JJF had speaker and consultant fees with GlaxoSmithKline, Novartis, Lundbeck, Solvay, Abbott, Bial, Grunenthal, and Merck Sharp and Dohme.

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The risk of infection with new oral anticoagulants: A meta-analysis

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Dear Editor,

The case report written by Stöllberger and Finsterer, has elicited a very interesting question: Is rivaroxaban associated with an increased risk of infection [1]? The authors have supported this hypothesis mainly on basic science studies (referring to the role of thrombin in the immune response) [2] and on observational data evaluating wound complications after orthopedic surgery [3]. Therefore, we thought that is would be of interest to further evaluate the overall risk of infections with the new oral anticoagulants (NOAC) in general and with rivaroxaban in particular, based on prospective randomized controlled clinical data.

To explore this hypothesis, we performed an electronic literature search (Medline and CENTRAL until November 2013) to identify phase

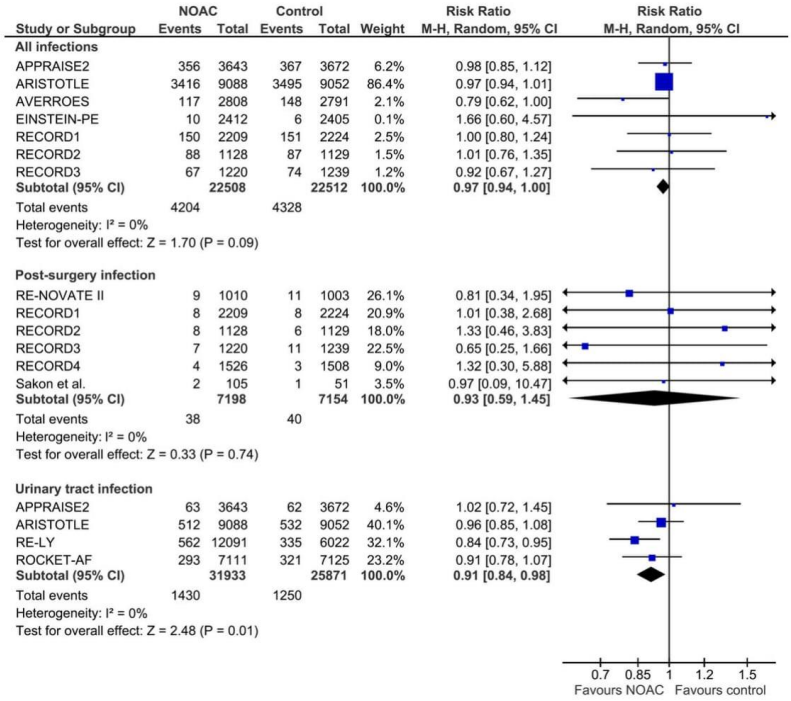

Fig. 1. Forest plot of infections' risk with NOAC.

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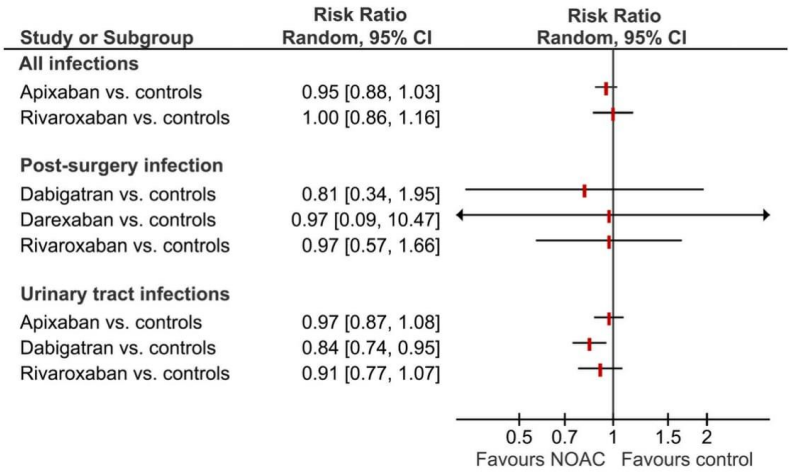

Fig. 2. Results of individual NOAC.

III randomized controlled trials (RCTs) of NOAC (apixaban, dabigatran, darexaban, edoxaban and rivaroxaban). We included for analysis RCTs that reported data on infections (independent of its origin), urinary tract infections and post-surgery infections. Furthermore we also looked for public reports of these drugs at the European Medicine Agency and Food and Drugs Administration sites.

We found 12 RCTs, enrolling 82,572 patients (44,351 exposed to NOACs and 38,221 exposed to control), that reported at least one of the pretended outcomes [4–15]. Mean follow-up ranged from 1 month to 2 years. We pooled the results from these RCTs through random effects meta-analysis (Fig. 1) to retrieve NOAC's global relative risks (RR) of infections. Pooled results for all NOAC did not show an increase risk of infection (RR 0.97; 95% CI 0.94 to 1.00; $p = 0.09$) or post-surgery/wound infection (RR 0.93; 95% CI: 0.59 to 1.45; $p = 0.74$). No heterogeneity was found among study results ($I^2 = 0\%$). Interestingly, NOACs were associated with a significant 9% risk reduction of urinary tract infection rate (RR 0.91, 95% CI: 0.84 to 0.98; $p = 0.01$; $I^2 = 0\%$).

We further evaluated each NOAC individually and none was associated with an increased risk of infection (Fig. 2).

In conclusion, the available randomized controlled data do not support the hypothesis of an increased infectious risk among patients treated with NOAC, including rivaroxaban. We recognize that this analysis is limited by the potential selective reporting bias (opportunistic reporting of infectious adverse events) as these outcomes were not predefined. Pooling the results at study-level also increases the risk of bias particularly when different populations are included in the analysis. It is probably unrealistic to expect that new RCTs will be conducted to definitely answer this question. Therefore, the risk of infection associated with NOAC should be properly addressed in large prospective cohort studies.

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SYSTEMATIC REVIEW

Tolerability and Acceptability of Non-Vitamin K Antagonist Oral Anticoagulants in Atrial Fibrillation: Systematic Review and Meta-Analysis

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Abstract

Background The non-vitamin K antagonist oral anticoagulants (NOACs) overcame some limitations of vitamin K antagonists (VKAs), and are at least as effective in stroke prevention, with an additional decrease of intracranial bleeding risk. The transferability of these benefits to the real world requires tolerability (related to adverse events) and acceptability (drug discontinuation) profiles at least similar to VKAs.

Methods We performed a systematic review with meta-analysis of randomized controlled trials (RCTs) evaluating NOACs versus VKAs in patients with non-valvular atrial fibrillation (AF). Studies were searched in April 2015 through MEDLINE, the Cochrane Collaboration's Database, Health Technology Assessment (HTA), Web of Science, and regulatory agencies' documents. Serious adverse events (SAEs) as well as drug-related and patient-related discontinuation rates were the outcomes of interest. Random-effects meta-analysis was performed, and the results expressed as risk ratios (RRs) and 95 % confidence intervals (CIs). Heterogeneity was evaluated with I^2 test.

Results Five RCTs evaluating four NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) and 72,720 patients were included. Overall, NOACs were associated with a 4 % risk reduction of SAEs (95 % CI 2–6; $I^2 = 0$ %). Drug-related and patient-related discontinuation rates were similar between NOACs and VKAs (RR 1.03 [0.88–1.21] and RR 0.99 [0.89–1.10], respectively). Significant heterogeneity ($I^2 \geq 75$ %) was found among studies results, which could be, at least partially, explained by the findings of the open-label dabigatran trial.

Conclusions NOACs were associated with a small, yet significant, risk reduction of SAEs in patients with AF. NOACs' drug-related and patient-related acceptability profiles were similar to those for VKAs. The results were heterogeneous mainly because of the increased rate of discontinuation associated with dabigatran. Pragmatic trials and cohort studies should be conducted to further address these important clinical questions.

Key Points

Non-vitamin K antagonist oral anticoagulants (NOACs) reduced significantly the risk of any serious adverse event.

Treatment discontinuation rates were similar between NOACs and warfarin, but there was substantial heterogeneity, mostly related to the RE-LY trial.

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Adis

1 Introduction

The non-vitamin K antagonist oral anticoagulants (NOACs), such as apixaban, dabigatran, edoxaban, and rivaroxaban were recently licensed for the prevention (after hip or knee arthroplasty) and treatment of venous thromboembolism, as well as for stroke and systemic embolism prevention in patients with non-valvular atrial fibrillation (NVAF). While venous thromboembolism treatment or prevention may require only temporary anticoagulant treatment [1, 2], stroke prevention in atrial fibrillation (AF) demands life-long treatment. As in any chronic treatment, its effectiveness depends on tolerability and patients' adherence to the medication.

In randomized controlled trials (RCTs), NOACs were at least as effective as vitamin K antagonists (VKAs) in preventing stroke and systemic embolism, and were associated with a decreased risk of intracranial bleeding [3]. They have overcome many other limitations of VKAs, namely the variability in dose response and the convenience related to absence of frequent coagulation monitoring and dose adjustments.

However, these life-long potential clinical benefits only outweigh the limitations if the adverse reactions and medication adherence profile is at least similar to that experienced by patients treated with VKAs. In the present systematic review, we aimed to evaluate the tolerability and acceptability of NOACs in patients with AF, as these patients require long-term anticoagulation.

2 Methods

Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) framework guidelines were used for reporting guidance [4].

2.1 Search Strategy

We searched MEDLINE (Ovid), the Cochrane Collaboration's Database (Ovid), Health Technology Assessment (HTA), and ISI Web of Science, all until April 2015. The search strategy was adapted from the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in humans [5], and is detailed in the supplementary electronic material (see online resource 1). Food and Drug Administration (FDA) and European Medicines Agency (EMA) reports were also consulted for additional unpublished data. Reference lists of retrieved studies and review papers were also cross-checked.

2.2 Study Selection (Eligibility Criteria) and Data Collection

We searched for RCTs comparing NOACs with VKAs. We only considered for analysis phase III RCTs because we aimed to determine the risk associated with the approved and commonly used doses of the NOACs and to avoid bias in risk estimation due to the impact of small size underpowered studies on meta-analysis results [6–9]. Furthermore, phase II RCTs have small follow-up periods, which undermines the aim of our review, which is to evaluate the acceptability and tolerability in patients with AF (requiring long-term anticoagulation). Studies where acetylsalicylic acid was used as a single control arm were excluded.

Patients included in studies were required to have a diagnosis of AF with an indication for anticoagulation. Patients with atrial flutter were also included because the procedures in terms of risk stratification and anticoagulation should be the same as in atrial fibrillation. Studies had to report detailed data about serious adverse events (SAEs) and reasons for drug discontinuations. The titles and abstracts of obtained records were screened independently by two authors. Doubts and disagreements were solved by a third person. Selected studies were assessed in full-text to determine their appropriateness for inclusion. Data about study design, patients' characteristics, interventions, and data of required outcomes were retrieved.

Quality of reporting was independently analyzed using the Cochrane Collaboration's Tool [10], which evaluates the following items: random sequence generation method, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, description of withdrawals and other risk of bias features deemed to be important by investigators.

2.3 Outcome Measures

The outcomes of interest were tolerability and acceptability of NOACs.

Tolerability was indirectly evaluated by determining the incidence of any SAE, as reported by investigators and/or adjudicated by committees. Whenever possible, treatment-emergent SAEs were retrieved.

Acceptability was split into drug-related (also associated with the tolerability profile) and patient-related treatment discontinuation [11]. Discontinuations due to adverse events were considered to be drug related, and discontinuations due to patients' own decisions (consent withdrawal and treatment discontinuation) were considered to be patient related. Whenever possible, the denominator of these outcomes was the safety population of each arm (i.e., patients that took the drug).

2.4 Statistical Analysis

Statistical analyses were performed using RevMan 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Individual studies and meta-analysis estimates were derived and presented in forest plots.

For the meta-analysis, we used the random-effects model weighted by the inverse-variance method to estimate pooled risk ratios (RRs) and 95 % confidence intervals (CIs) [12]. This method was used by default independently of the heterogeneity of the pooled analysis. RRs were chosen to report the results because relative measures tend to be more similar across studies than absolute estimates in populations having different baseline characteristics and lengths of follow-up [13]. Results were evaluated through Z test, and these were considered significant if $p < 0.05$.

Heterogeneity, defined as variation beyond chance, was evaluated through the I^2 test that measures the percentage of total variation between studies [14]. Heterogeneity was considered to be substantial if $I^2 \geq 50$ %.

When results were statistically significant, we calculated the number of patients needed to treat (NNT) to expect the avoidance of one event, and the number of events avoided per 1000 treated patients, using as baseline risk the event rate reported in VKA-treated patients [15, 16].

Because of the expectation of inclusion of both open-label and blinded RCTs, and considering the possible influence of these characteristics in the analyzed outcomes, we prespecified a subgroup analysis according to the blinding status of included trials [17]. Despite the distinctive pharmacokinetic and pharmacodynamic properties of individual NOAC drugs, we hypothesized that these drugs could have a class effect compared with VKAs, as shown for some outcomes (e.g., intracranial hemorrhage). Therefore, we did not plan an a priori subgroup analysis considering each individual NOAC drug.

Publication bias was assessed through visual inspection of funnel plots asymmetry. Egger and Peters tests were performed to assess objectively this risk [18, 19].

3 Results

3.1 Results of the Search and Description of Studies

After a comprehensive search for RCTs fulfilling our eligibility criteria, we were able to include five phase III RCTs evaluating four NOACs: apixaban, dabigatran, edoxaban, and rivaroxaban (two studies with rivaroxaban) [20–24].

Supplementary Figure 1 shows the flowchart of study selection, with the reasons for study exclusion (see online resource 1).

Altogether, these trials enrolled 72,720 patients with NVAF under oral anticoagulant treatment, 59 % of them treated with NOACs. Supplementary Table 1 details the main characteristics of included studies.

Overall, the risk of bias was moderate according to the qualitative Cochrane Collaboration Tool (Supplementary Figure 2). We considered that all trials had a high risk of selective reporting because the reporting of any adverse event and its degree is prone to such bias. Additionally the randomized evaluation of long term anticoagulant therapy with dabigatran etexilate (RE-LY) trial had an open-label design [21].

3.2 Tolerability and Acceptability

NOACs were associated with a small yet significant 4 % risk reduction of SAEs in patients with NVAF (RR 0.96; 95 % CI 0.94–0.98; Fig. 1a). The results were consistent across studies, without any statistical heterogeneity ($I^2 = 0$ %). NNT with NOACs to expect the prevention of one SAE compared with VKAs was 74 (95 % CI 49–148) for an average period of 1.7 years. For each 1000 patients treated with NOACs instead of VKAs, it is expected that 14 SAEs (95 % CI 7–20) would be prevented for an average period of 1.7 years.

The drug discontinuation rate due to adverse events was similar between NOACs and VKAs (RR 1.03; 95 % CI 0.88–1.21; Fig. 1b). This analysis was remarkable for significant statistical heterogeneity ($I^2 = 93$ %).

Patient-related drug discontinuation was also similar between NOACs and VKAs (RR 0.99; 95 % CI 0.89–1.10; Fig. 1c), again showing significant statistical heterogeneity ($I^2 = 75$ %).

3.3 Subgroup Analysis According to Study Design

The RE-LY study (dabigatran vs. VKA) was the only open-label trial [21]. The risk reduction of SAEs was not different between blinded and open-label RCTs ($p = 0.49$; Table 1).

For both drug- and patient-related treatment discontinuations, the results for dabigatran versus VKA (derived from the open-label RE-LY trial) were significantly different compared with the pooled results for the other NOACs ($p < 0.0001$ and $p = 0.0001$, respectively). Dabigatran was associated with a significant increase of both drug- and patient-related treatment discontinuations, while pooled results for the other NOACs versus VKAs showed a reduction in the risk of discontinuation due to either adverse events or patients' own decisions (Table 1). The RE-LY trial reported a high number of study discontinuations in dabigatran-treated patients due to gastrointestinal adverse events [21]. The level of heterogeneity in pooled estimates for discontinuation due to drug- and patient-related causes decreased when the RE-LY trial was removed from the analysis ($I^2 = 67$ % and $I^2 = 0$ %, respectively).

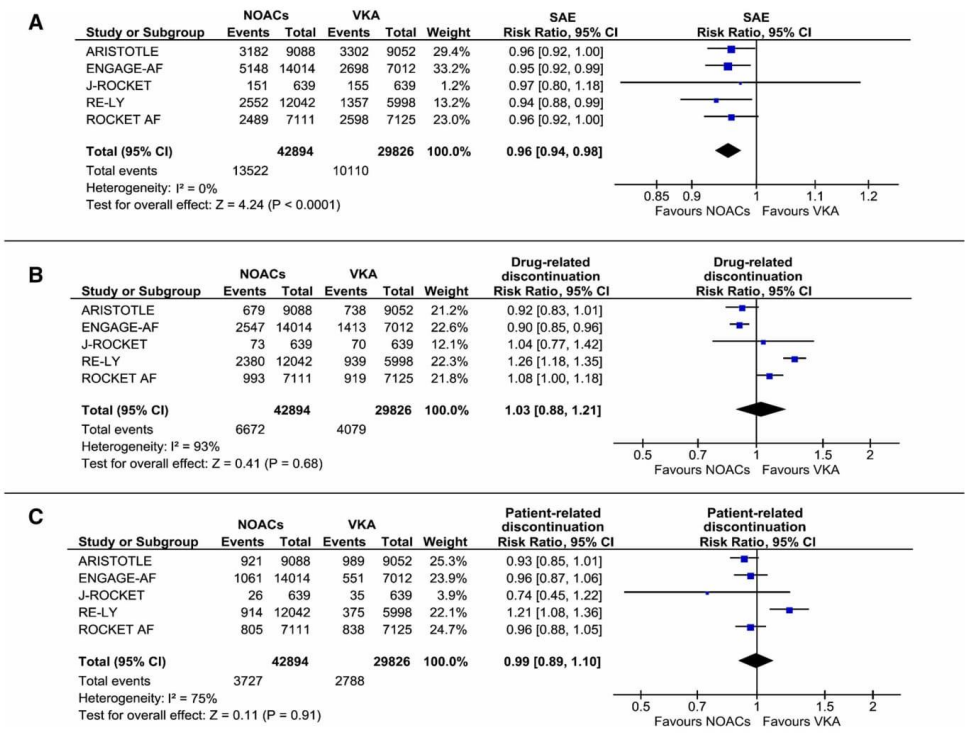

Fig. 1 Forest plot with meta-analysis for **a** SAE risk, **b** drug-related treatment discontinuation risk, and **c** patient-related treatment discontinuation risk. *ARISTOTLE* apixaban for the prevention of stroke in subjects with atrial fibrillation, *CI* confidence interval, *ENGAGE-AF* global study to assess the safety and effectiveness of edoxaban vs standard practice of dosing with warfarin in patients with atrial fibrillation, *J-ROCKET* rivaroxaban versus warfarin in Japanese patients with non-valvular atrial fibrillation, *NOAC* non-vitamin K antagonist oral anticoagulant, *RE-LY* randomized evaluation of long term anticoagulant therapy with dabigatran etexilate, *ROCKET-AF* an efficacy and safety study of rivaroxaban with warfarin for the prevention of stroke and non-central nervous system systemic embolism in patients with non-valvular atrial fibrillation, *SAE* serious adverse event, *VKA* vitamin K antagonist

Table 1 Results of analysis according to study design

Trial design	RCT/patients	SAE			Drug-related discontinuation			Patient-related discontinuation		
		RR [95 % CI]	I^2	*p* value for interaction	RR [95 % CI]	I^2	*p* value for interaction	RR [95 % CI]	I^2	*p* value for interaction
Double-blinded RCTs	4/54,680	0.96 [0.94–0.98]	0 %	0.49	0.95 [0.87–1.04]	67 %	<0.0001	0.95 [0.90–0.99]	0 %	<0.0001
Open-label RCT	1 (RE-LY)/ 18,040	0.94 [0.88–0.99]	N/A		1.26 [1.18–1.35]	N/A		1.21 [1.08–1.36]	N/A	

CI confidence interval, *RCT* randomized controlled trial, *RR* risk ratio, *SAE* serious adverse event, *NA* not available

We further performed an exploratory analysis by adding both drug- and patient-related treatment discontinuations into a single outcome. As expected, overall NOACs did reduce the incidence of this outcome (RR 1.00; 95 % CI 0.88–1.14; Supplementary Figure 3), with high heterogeneity ($I^2 = 95$ %), mostly due to RE-LY (RR 1.25; 95 % CI 1.18–1.32). Without RE-LY, NOACs showed a 5 % reduction of drug discontinuation risk (RR 0.95; 95 % CI 0.90–1.00; $I^2 = 57$ %; Supplementary Figure 3).

3.4 Publication Bias

The scarcity of studies makes funnel plot evaluation less precise for risk of publication bias assessment [25]. Therefore, we only performed Egger and Peters tests, and these were not suggestive for publication bias ($p \geq 0.25$ for all outcomes and statistical tests).

4 Discussion

NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are associated with a small, yet clinical significant, decrease in the risk of SAEs when compared with VKAs, without differences between drugs, suggesting a drug-class effect regarding this outcome. However, acceptability, as evaluated through the rate of treatment discontinuation (whether drug related or patient related) was heterogeneous, but not different from VKAs.

The results found among SAEs may be clinically relevant as they reflect differences in the tolerability profile, with lower risk of events with NOACs. Despite the different criteria attributable to the seriousness of an adverse event, among other reasons, these are related to fatal or life-threatening events, disabilities, or situations that require or prolong hospitalization. Therefore, a reduction of events associated with such outcomes may decrease the burden associated with anticoagulated NVAF patients.

Chatterjee et al. [26] have published a review evaluating treatment discontinuations with NOACs. They concluded that NOACs (vs. placebo) had a higher rate of drug discontinuation in patients with acute coronary syndrome. However, NOACs were not significantly different from those with conventional drugs in terms of drug discontinuation in NVAF and venous thromboembolism patients [26]. In our review, different to Chatterjee and colleagues, we considered edoxaban data (ENGAGE AF-TIMI 48: Global study to assess the safety and effectiveness of edoxaban vs standard practice of dosing with warfarin in patients with atrial fibrillation) and excluded studies that could increase bias and decrease precision, such as phase II RCTs and acetylsalicylic acid-controlled trials. Furthermore, we concluded that NOACs decrease the risk of SAEs, which is an important addition to the current knowledge.

It is known that complex therapeutic regimens are important risk factors for non-adherence [27, 28]. It is conceivable that NOACs could improve patients' acceptance of anticoagulants due to their dose-response predictability and not requiring frequent dose adjustments or assessment of hemostasis parameters. Most of the trials had a double-blinded design, and patients allocated to NOACs were also treated with sham warfarin and INR monitoring. Therefore, the results retrieved from those trials do not account for the potential benefits of NOACs convenience. In terms of drug-related discontinuation, and with the exception of dabigatran, NOACs showed an acceptability overlapping that of VKAs. In the RE-LY study, patients treated with dabigatran had higher discontinuation rates. The knowledge about the treatment assigned in RE-LY can, at least partially, explain these findings because patients who know that they are being treated with a new active drug may be more prone to discontinue in the setting of an adverse event. However, the discontinuation rate in the dabigatran group due to adverse events was also significantly higher compared with standard anticoagulation in the double-blinded double-dummy efficacy and safety of dabigatran compared to warfarin for 6 month treatment of acute symptomatic venous thromboembolism (RE-COVER) trial that enrolled patients with venous thromboembolism (hazard ratio 1.33; 95 % CI 1.01–1.76; $p = 0.05$) [29]. Gastrointestinal symptoms, namely dyspepsia, were the main reason for premature dabigatran discontinuation. Other interventions (e.g., taking the drug with meals, H_2 antagonists or proton-pump inhibitors) may be needed to mitigate these symptoms in order to improve gastrointestinal tolerability and drug-related acceptability. Our analysis is relevant to establishing the overall tolerability profile of drugs and to generate information/signs about any suspicious adverse events [30–32].

Concerning patient-related discontinuation (acceptability), no differences were found between NOACs and VKAs (RR 0.99; 95 % CI 0.89–1.10), but excluding the RE-LY trial (open-label study) from the analysis resulted in a 5 % significant reduction of patient-related discontinuation risk with NOACs (RR 0.95; 95 % CI 0.90–0.99). The authors do not have an obvious reason for the higher rate of patient-related discontinuation among dabigatran-treated patients (RR 1.21; 95 % CI 1.08–1.36), as well as for drug-related discontinuation (RR 1.26; 95 % CI 1.18–1.35). It may be hypothesized that the open-label design, by revealing to the patients which treatment they were taking, may have led some patients to choose to maintain their previous standard treatment, but venous thromboembolism data (double-blinded RCT) does not support it [29]. Other hypotheses can be related to the reporting of a patient's own motifs having (elicited or not) drug-related symptoms.

This is clinically relevant because oral anticoagulant discontinuation (or switch) is associated with a higher risk of thromboembolic events [33].

4.1 Limitations

At outcome level, selective reporting bias was our main concern considering the evaluation of SAEs. SAEs are always clinically relevant, but are diverse and may not be related to studied drugs. Some studies reported details on SAEs, while others were more detailed on frequent adverse

events (not SAEs). These differences did not allow comparing indirectly NOACs' individual SAEs. Furthermore, only ROCKET-AF (An efficacy and safety study of rivaroxaban with warfarin for the prevention of stroke and non-central nervous system systemic embolism in patients with non-valvular atrial fibrillation) provided data about treatment-emergent SAEs, the while other studies only supplied information about overall adverse events.

Heterogeneity of clinical characteristics (e.g., comorbidities that may influence drug dosages, such as renal dysfunction) and interventions (different NOACs, the same NOAC at different dosages, and the possibility of different co-medications) across the various studies should also be considered. The statistical heterogeneity found in some outcomes is a further limitation. Exploring the potential sources of such heterogeneity, we found that dabigatran showed a different acceptability profile to other NOACs. Nevertheless, the reported NOAC results (with or without dabigatran) were consistent in terms of direction and significance of estimates (acceptability profile similar to that for VKAs).

Finally, we accessed tolerability and acceptability on the basis of data from exploratory clinical trials in a tightly controlled environment. These outcomes are better evaluated in pragmatic trials and from "real-world" data.

5 Conclusions

Overall, NOACs are associated with a small, yet potentially clinically significant, 4 % reduction in the risk of SAEs. NOACs' drug-related and patient-related acceptability profiles were similar to those for VKAs. At this level, NOACs did not show a clear drug-class effect. The results were heterogeneous mainly because of the increased rate of discontinuation in dabigatran-treated patients (predominantly associated with gastrointestinal symptoms). These conclusions are driven from randomized data, which is not the most powerful design to evaluate safety, tolerability, and acceptability outcomes. Pragmatic trials and large prospective cohort studies should be conducted to address these important clinical questions.

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ORIGINAL ARTICLE

Burden of disease and cost of illness of atrial fibrillation in Portugal☆

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Disability-adjusted life years

Abstract
Introduction and Objectives: Atrial fibrillation is the most prevalent sustained arrhythmia. This paper estimates the burden and cost of illness attributable to atrial fibrillation in Portugal based on demographic and health statistics.
Methods: Mortality data by cause of death came from the European Detailed Mortality Database of the World Health Organization (WHO). Hospital data were taken from the Portuguese diagnosis-related groups database. The burden of disease was measured using DALYs (disability-adjusted life years), a metric adopted by the WHO. Costs studied included resource use and lost productivity. The burden and cost of illness are those attributable to atrial fibrillation and its main complication, ischemic stroke.
Results: In Portugal, 4070 deaths were attributable to atrial fibrillation in 2010, corresponding to 3.8% of all deaths. In total, the burden of disease attributable to atrial fibrillation was estimated at 23 084 DALYs: 10 521 resulting from premature deaths (1.7% of the total DALYs due to death in 2010 in Portugal), and 12 563 resulting from disability. The total estimated direct costs attributable to atrial fibrillation at 2013 prices were €115 million: €34 million for inpatient care and €81 million for outpatient care. Indirect costs resulting from lost production due to disability were estimated at €25 million.

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Conclusions: Atrial fibrillation has an important social impact in Portugal due to its associated mortality and morbidity, and was responsible in 2013 for a total cost of €140 million, about 0.08% of gross domestic product.

PALAVRAS-CHAVE
Fibrilhação auricular;
Doença cerebrovascular;
Custo e carga da doença;
Anos de vida perdidos ajustados por incapacidade

Carga e custo da fibrilhação auricular em Portugal

Resumo
Introdução e objetivos: A fibrilhação auricular é a disritmia persistente mais prevalente. Pretendemos estimar a carga e custos da doença atribuíveis à fibrilhação auricular em Portugal com base nas estatísticas demográficas e de saúde.
Métodos: Utilizou-se informação sobre mortalidade por causa da OMS-Europa. Dados hospitalares foram provenientes da base de dados dos GDH. A carga da doença foi medida pelos DALY (*disability-adjusted life years*) ou anos de vida perdidos ajustados por incapacidade, uma métrica adotada pela Organização Mundial de Saúde. Os custos incluíram os consumos de recursos e as perdas de produtividade. A carga e os custos da doença estimados são os atribuíveis à fibrilhação auricular e à sua principal complicação, o acidente vascular cerebral isquémico.
Resultados: Em Portugal, no ano 2010, podem atribuir-se à fibrilhação auricular 4070 mortes correspondendo a 3,8% do total das mortes ocorridas. A carga da doença atribuível à fibrilhação auricular foi estimada em 23.084 DALY: 10.521 decorrentes das mortes prematuras (1,7% dos DALY por morte em Portugal em 2010) e 12 563 devidos à incapacidade gerada pela morbilidade. O total estimado de custos diretos para o sistema de saúde a preços de 2013 atribuíveis à fibrilhação auricular foi de 115 M€ (milhões de euros): 34 M€ em internamento e 81 M€ em ambulatório. Os custos indiretos gerados pela produção perdida devidos à incapacidade causada pela doença foram estimados em 25 M€.
Conclusões: A fibrilhação auricular tem um importante impacto social em Portugal devido à mortalidade e morbilidade geradas, podendo-se-lhe atribuir em 2013 um custo total de 140 M€, cerca de 0,08% do produto interno bruto.

List of abbreviations

AF	atrial fibrillation
DALY	disability-adjusted life year
DRG	diagnosis-related group
ICD 9-CM	International Classification of Diseases, Ninth Edition, Clinical Modification
MI	myocardial infarction
NHS	national health service
PAF	population attributable fraction
RR	relative risk
WHO	World Health Organization

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia. It was estimated in 2010 that 33.5 million individuals worldwide,[1] and nearly nine million individuals in the European Union (EU),[2] had AF; the number in the EU is predicted to double to nearly 18 million by 2060. AF is associated with advanced age, male gender and various comorbidities including hypertension, heart failure, valve disease and coronary artery disease.[3–7]

AF can be silent, only being diagnosed when a complication develops.[8,9] The main complication is systemic thromboembolism leading to stroke; AF patients are at 3–5 times higher risk of ischemic stroke, and more severe stroke.[7,10–14] It is estimated that 14% of AF patients in Portugal have suffered stroke. AF is thus an important cause of mortality and morbidity in itself and due to the associated risk of ischemic stroke.[15]

Against this background, it is important to assess the economic impact and burden and cost of illness of AF in Portugal, which is the aim of the present study.

The purpose of studies on cost of illness is to measure the impact of a disease or risk factor in terms of use of economic resources and reduction in economic activity due to associated disability. Studies on burden and cost of illness are not strictly speaking economic evaluations, since they do not address specific interventions or compare alternative

interventions; rather, they seek to paint an accurate picture of a particular health problem and its magnitude.

Despite the importance of such studies, few have been carried out in Portugal.[16,17] In particular, there has been no study of the burden and cost of AF, but the limited information at the international level[18,19] suggests that the costs involved are high.

Epidemiology of atrial fibrillation: incidence and prevalence

Estimates of the incidence and prevalence of AF vary considerably between different sources, depending on population characteristics and diagnostic criteria.[20] Furthermore, since AF can be asymptomatic, the reported incidence and prevalence may be underestimated.[20,21]

Incidence

The incidence of AF in the main European and American studies ranges between 0.1/1000 person/years in women aged 20–54 years and 40/1000 person/years in men aged ≥80 years and 69/1000 person/years for individuals aged ≥90 years.

Incidence increases progressively with age[5]; from age 50 onward it doubles for each decade.[20] It is also higher in males in all age-groups (men are 1.5 times more likely to develop AF),[22] although some authors report that this difference is smaller in older age-groups.[20] A population-based cohort in the USA shows that the incidence is increasing.[23]

In the absence of studies estimating AF incidence in Portugal, the best source is the Rotterdam study,[6,24] a prospective European study that analyzes the relevant age-groups; it has accordingly been used to calculate the burden of disease in the present study.

Prevalence

The main source of information on the prevalence of AF in Portugal is the FAMA study,[5] a cross-sectional study of a representative sample of the Portuguese population aged 40 and over that included 10 477 individuals, 55% female, with a median age of 58 years. The estimated prevalence was 2.5% (95% confidence interval: 2.2%–2.8%), increasing with age (significantly higher in individuals aged 70 and over) but with no significant differences between the sexes or geographical regions.

Only 1.6% of the FAMA study population said they had been diagnosed with AF. Regarding previous clinical events, there were significant differences between the general population and individuals with AF in terms of history of stroke and myocardial infarction (MI) (stroke: 5% vs. 14%, $p<0.001$; MI: 3% vs. 10%, respectively; $p<0.001$).

Methods

Burden of disease

Burden of disease is estimated by means of disability-adjusted life years (DALYs), a measure of the years of health lost due to disease or premature death. It includes two time-based indicators: years of life lost, the difference between age at death and standard life expectancy for that age; and years lost due to disability.[25] Disability is assigned a severity weight between 0 (no disability; perfect health) and 1 (total disability or death). These weights were originally defined by expert panels at the World Health Organization (WHO), and were re-estimated for the Global Burden of Disease Study 2010 through a large-scale empirical investigation.[27] The formula used is:

$$DALY = \int_{a}^{a+L} DCxe^{-\beta x}e^{-r(x-a)}dx$$

where:

a – age of onset,
L – duration of disability or time lost due to premature mortality,
D – disability weight (between 0 and 1),
C – age-weighting correction constant (0.04),
e – expectation of life,
x – age (ranging between a and a+L),
β – parameter from the age-weighting function (0.1658), and
r – discount rate (3%).

The discount rate used in this calculation is 3%, and the calculation includes different weighting for different age-groups, with the middle age-group (20–50 years), the years when people tend to be raising children, being assigned greater weight.[25]

As there is no direct evidence available on the duration of diseases, information which is needed to calculate DALYs, we used the DisMod II model developed by Barendregt et al. for the WHO.[26] This exploits the causal relations between the variables that describe a disease process by age-group and gender: incidence, prevalence, remission, case fatality, mortality, relative risk (RR) for mortality, and duration.

The model was calibrated using data from the Portuguese Institute of Statistics on the resident population and mortality in Portugal for 2010, as well as the findings of the FAMA study (on AF prevalence) and the Rotterdam Study (on AF incidence). The remission rate of AF was assumed to be zero.

In order to calculate DALYs due to disability, the degree of disability attributable to a given health problem must be specified. The weighting factors used to characterize the relevant conditions in this study were those published in the Global Burden of Disease Study 2010.[27]

Ideally, studies of burden of disease should refer to a specific year, but the heterogeneity of the information sources and the changes that the Portuguese national health service (NHS) has undergone in recent years mean that in practice it is more informative to use the most recent data available for each of the areas under study. Accordingly, the calculations were based on population and mortality statistics from the WHO for 2010, hospital data from 2011 and official NHS prices for 2013. The resulting figures are thus as up-to-date as possible.

Cost of illness

The first step in the analysis was to identify the conditions that are related to AF as well as the disease itself. The main complications of AF are heart failure and ischemic stroke, the latter being the most serious.[28,29] The relation between AF and stroke is unequivocal: patients with AF have an age-adjusted risk that is five-fold higher than the general population, and stroke in AF patients is more likely to lead to severe disability.[30] With regard to intracranial hemorrhage, the risk is similar to that of the general population, but it is higher in AF patients under anticoagulant therapy.[30,31]

The conditions considered in the analysis were AF and ischemic stroke, identified by the International Classification of Diseases, Ninth Edition, Clinical Modification (ICD 9-CM) codes 427.31 (Atrial fibrillation), 427.32 (Atrial flutter), 433 (Occlusion and stenosis of precerebral arteries [with cerebral infarction]) and 434 (Occlusion of cerebral arteries [with cerebral infarction]).

The second step was to establish the quantitative relation between AF and stroke by estimating the fraction of the cost and burden of stroke that statistically is due to AF, using the epidemiological concepts of RR and population attributable fraction (PAF). RR in this case is the ratio between the risk of suffering stroke in a population with AF and the risk in a population without AF. The values for RR used in this study, taken from Kannel et al.,[32] based on data from the Framingham Study and recently updated by Ball et al.,[7] were 4.0 (50–59 years), 2.6 (60–69 years), 3.3 (70–79 years) and 4.5 (80–89 years).

According to Lin et al.,[11] also based on the Framingham Study, mortality following stroke was significantly higher if the stroke was AF-related (25% vs. 14%; RR: 1.79). On the basis of this information and the RRs presented above, the RR for death due to stroke was estimated for a population with AF in comparison with a population without AF: 7.2 (50–59 years), 4.7 (60–69 years), 5.9 (70–79 years) and 8.1 (80–89 years).

The PAF is the proportion of cases that would not occur in a population if the risk factor were eliminated and can be calculated by the equation[33]:

$$PAF = \frac{P(RR-1)}{P(RR-1)+1}$$

where:

PAF – population attributable fraction,
P – prevalence of AF, and
RR – relative risk of patients with AF suffering stroke.

On the basis of the estimates of AF prevalence in Portugal and the RRs presented above, the fractions of stroke and death from stroke attributable to AF were calculated (Table 1). For example, in men aged over 80, the prevalence of AF is 7.4% and the RR of stroke is 4.5, and so the proportion of the burden of disability and costs of stroke (the PAF) attributable to AF is 20.57%.

Direct costs attributable to atrial fibrillation

As well as the burden of disease, AF is also responsible for costs to society and to the NHS, considered as direct costs attributable to atrial fibrillation, which in this study are divided between inpatient and outpatient care.

Costs of inpatient care. The centrally managed database of diagnosis-related groups (DRGs) of the Portuguese NHS for 2011 was used to estimate resource use for inpatient care, including other interventions covered by the DRGs such as outpatient surgery and day hospital sessions arising from AF and associated conditions.

Hospitalizations were identified on the basis of a primary diagnosis of AF or of ischemic stroke in accordance with the ICD 9-CM.

The unit costs used in the analysis were taken from Order in Council 163/2013, which defines the prices associated with DRGs and other health interventions. The costs of AF- and stroke-related admissions were calculated by summing the product of the number of patients in each DRG and the price of the corresponding DRG.

Costs of outpatient care. Outpatient costs include direct medical costs (consultations, emergencies, diagnostic and therapeutic interventions, drugs, physiotherapy sessions, etc.), and direct non-medical costs (urgent and non-urgent patient transportation and institutionalization).

It is considerably more difficult to estimate outpatient costs than inpatient costs with any precision, since there is no equivalent database on which to calculate the relevant resource use. Resource use was estimated on the basis of the literature and on the findings of a panel of experts from various medical specialties convened to define resource use in patients with AF and ischemic stroke.

Most of the resources identified were for AF patients both with and without ischemic stroke, and so simply adding them together would result in double counting. To avoid this error, the numbers of patients in each of these two groups were calculated by applying the PAF to the population with ischemic stroke (columns 6 and 7 in Table 1). The patterns of resource use for the two groups were thus determined separately and then multiplied by the corresponding number of patients.

In calculating outpatient resource use, it is important to consider only patients with diagnosed AF. According to the FAMA study,[5] 36% of cases of AF in patients aged 40 and over are undiagnosed, and so calculation of the outpatient resource use was based on the prevalence of diagnosed AF. However, to appreciate the wider picture, it should be borne in mind that the prevalence of diagnosed AF in Portugal is increasing, as in other European countries, probably due to aging populations and better diagnosis.[30]

Indirect costs of atrial fibrillation

In calculating the indirect costs of AF, only costs associated with lost production due to the disease were included (excluding losses due to premature death).

The first step in the calculation was to estimate how AF affects employment in different age-groups and by gender. The employment rates for the general population were based on data from the Portuguese Institute of Statistics for the second half of 2013. The daily monetary value corresponding to loss of production was calculated using a human

Table 1 Fraction of stroke and death from stroke attributable to atrial fibrillation.

Age-groups (years)	RR of stroke	RR of death from stroke	Prevalence of AF		Fraction of stroke attributable to AF (%)		Fraction of death from stroke attributable to AF (%)	
			Male	Female	Male	Female	Male	Female
40–49	4.0[a]	7.2[a]	0.1	0.2	0.30	0.60	0.62	1.22
50–59	4.0	7.2	1.7	0.4	4.85	1.19	9.54	2.42
60–69	2.6	4.7	1.6	1.6	2.50	2.50	5.56	5.56
70–79	3.3	5.9	8.2	5.5	15.87	11.23	28.83	21.37
80+	4.5	8.1	7.4	11.9	20.57	29.40	34.44	45.80

AF: atrial fibrillation; RR: relative risk.
[a] The same RR was assumed for the 40–49 year age-group as for the 50–59 year age-group.

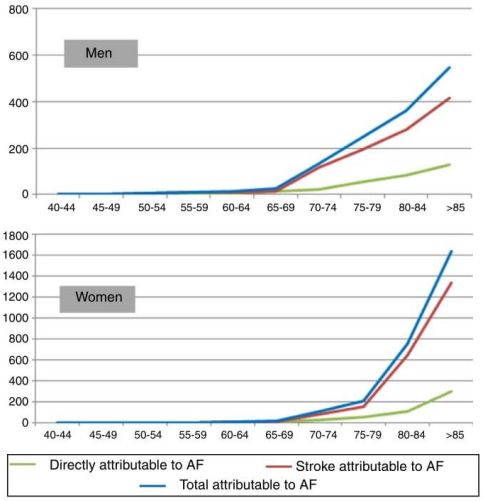

Figure 1 Mortality attributable to atrial fibrillation by age-group and gender. AF: atrial fibrillation.

capital approach, on the basis of average daily labor costs, including employers' contributions to social insurance.[34] To calculate the total costs at 2012 prices of lost productivity, the mean daily labor costs for 2012 were estimated on the basis of data for 2009 (the last year for which official figures are available from the Ministry of Labor and Social Security) and the mean annual increases in earnings between 2009 and 2012 from the Office for Strategy and Planning of the same Ministry. Since the aim was to calculate the cost of productivity lost per day due to AF, the average annual labor costs were divided by 230 working days, resulting in an estimate of €96.53 in 2012 for the age-groups under consideration, and the total indirect costs attributable to AF were estimated on this basis. Since earnings remained stable between 2012 and 2013, this figure was considered appropriate to represent indirect costs in 2013.

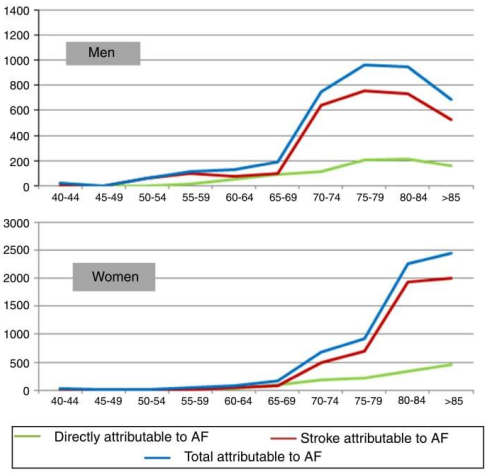

Figure 2 Disability-adjusted life years due to death attributable to atrial fibrillation by age-group and gender. AF: atrial fibrillation.

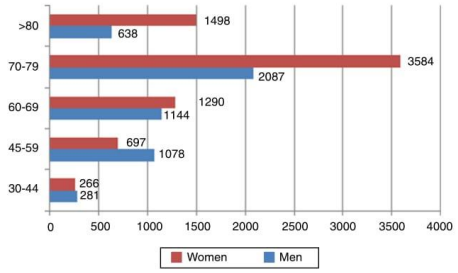

Figure 3 Disability-adjusted life years due to disability attributable to atrial fibrillation by age-group and gender.

Total indirect costs

The absenteeism due to ischemic stroke attributable to AF must be taken into account as well as that of AF itself. Calculation of the indirect costs of stroke directly attributable to AF requires use of the PAF (Table 1). Absenteeism related to AF and ischemic stroke may have different reasons but given the nature of AF, it is only ischemic stroke that leads to prolonged absence from work due to physiotherapy sessions and/or other reasons.

Results

Burden of disease

Disability-adjusted life years due to death

The first step in quantifying the burden of disease arising from mortality attributable to AF is to calculate the number of deaths and DALYs due to diseases associated

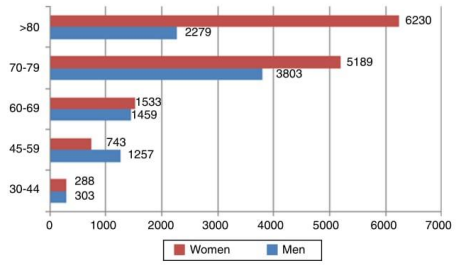

Figure 4 Total disability-adjusted life years attributable to atrial fibrillation by age-group and gender.

Table 2 Costs of inpatient care attributable to atrial fibrillation.

Disease	No. of episodes	Total cost (€)	PAF (%)	Attributable cost (€)
Inpatient DRGs				
AF	6339	17 569 100	100	17 569 100
Ischemic stroke	20 903	113 310 028	14	15 523 595
Outpatient DRGs				
AF	259	1 410 227	100	1 410 227
Ischemic stroke	4	6409	14	878
Subtotal				
AF	6598	18 979 327	100	18 979 327
Ischemic stroke	20 907	113 316 437	14	15 524 473
Total				34 503 800

AF: atrial fibrillation; DRG: diagnosis-related group; PAF: population attributable fraction.

with AF. Data on mortality from AF and stroke in Portugal were taken from the WHO's European Detailed Mortality Database (http://data.euro.who.int/dmdb/). Most deaths from stroke in this database are not specified as ischemic or hemorrhagic, so on the basis of the DRGs and the opinions of the expert panel, we estimated that 30% in women and 40% in men are hemorrhagic, and that in 2010 there were 813 deaths from AF (303 men and 510 women) and 9316 deaths from ischemic stroke.

On the basis of these data and the standard life expectancy by gender and age-group, DALYs due to death were calculated. We estimate that in 2010 33 753 DALYs were lost from deaths due to AF and stroke. Applying the PAF presented in Table 1 to the figures for mortality and DALYs from death due to stroke, the burden of stroke attributable to AF in Portugal in 2010 is estimated at 4070 deaths (3.8% of all deaths) and 10 521 DALYs due to death (1.7% of all DALYs from premature death). Figure 1 shows the distribution of deaths for men and for women by age-group.

Figure 2 shows the distribution of DALYs due to death attributable to atrial fibrillation by age-group and gender. Stroke was responsible for the majority of life years lost due to premature death attributable to AF in both sexes.

It can also be seen in Figure 2 that the distribution of burden of disease at more advanced ages differs markedly between men and women, mainly due to differences in the number of men and women in older age-groups. Thus, there are more DALYs due to death attributable to AF per 100 000 population in men up to the age of 79 (437 vs. 304 for women), but this pattern is reversed over the age of 80 (928 for men vs. 1446 for women).

Disability-adjusted life years due to disability

The severity weight for disability due to AF is 0.145. For stroke, two representative cases – moderately severe stroke with long-term sequelae (weight 0.076) and moderately severe stroke with long-term sequelae and cognitive deficit (weight 0.312) – were considered and the mean of the two (0.194) was adopted for this study.

It is estimated that 14% of AF patients in Portugal have suffered stroke. Calculation of the severity weight in these patients entails adding to the mean weight for AF (0.145) a part of the corresponding disability weight for stroke. The mean RR of stroke for the population with AF is 3.71. The proportion of stroke attributable to AF is (RR-1)/RR, hence the fraction of strokes in AF patients attributable to AF itself is 73.05%. Considering that 14% of AF patients have suffered stroke, the mean disability weight of AF is (0.145+0.14*0.7305*(0.194−0.145))=0.15. On this basis, AF caused a loss of 12 563 DALYs due to disability in 2010, over 5000 for men and over 7000 for women (Figure 3).

Adding DALYs due to premature death and due to disability gives a total burden of disease attributable to AF of 23 084 DALYs (Figure 4), of which DALYs due to disability account for around 54%.

Cost of illness

Direct costs

Costs of inpatient care. The DRG database was used to identify 6598 episodes with a primary diagnosis of AF and 20 907 with a primary diagnosis of ischemic stroke,

Table 3 Outpatient costs attributable to atrial fibrillation.

	No. of patients		Total cost (€)		
	Incidence-mortality	Prevalence-(incidence-mortality)	Year of diagnosis	Patients diagnosed in previous years	Total
AF	10 960	72 160	7 140 340	37 229 346	44 369 687
Stroke	2171	16 097	15 185 149	21 431 089	36 616 238
Total			22 325 489	58 660 435	80 985 925

AF: atrial fibrillation.

Table 4 Indirect costs attributable to atrial fibrillation.

	Consultations		Exams		Hospitalization and convalescence
	Year of diagnosis	Patients diagnosed in previous years	Year of diagnosis	Patients diagnosed in previous years	Year of diagnosis
No. of working days lost	2.17	1.66	1.68	1.3	6.5
Cost per patient (€)	52	40	40	31	60
Total annual indirect costs (€)	571 335	2 876 961	436 026	2 227 050	661 444
Total (€)					6 772 816

AF: atrial fibrillation.

corresponding to 31 and 23 different DRGs, respectively. Table 2 summarizes the total costs of inpatient care attributable to AF. The PAF of ischemic stroke used in the cost analysis is a population-weighted mean of the PAFs in Table 2. The total cost of inpatient care (including outpatient DRGs) attributable to AF is €34 503 800. The data shown in Table 2 reveal that the cost of hospitalization for AF itself accounts for 55% of all costs attributable to AF, with ischemic stroke accounting for the remainder.

Costs of outpatient care. Based on the resource use estimated by the expert panel and on unit costs, the outpatient costs attributable to AF and ischemic stroke were calculated for the year of the diagnosis or event and following years (Table 3). The total cost of outpatient care attributable to AF is around €22 million in the year of the diagnosis or event and €59 million for patients diagnosed in previous years. The outpatient cost attributable to AF accounts for 45.2% of the total costs attributable to AF.

The total direct costs attributable to AF are €115.5 million, made up of €34.5 million for inpatient care (Table 2) and €81 million for outpatient care (Table 3). Ischemic stroke is responsible for 45% of all direct costs attributable to AF.

Table 5 Indirect costs of ischemic stroke.

Percentage of patients	No. of patients	Scenario	Months of absenteeism	Costs per patient (€)	
				Consultations and exams	Physiotherapy sessions
Year of diagnosis					
13.08	270	No further care required after stay in stroke unit	0	94	0
11.79	244	Unable to return to work following discharge	12	0	5518
52.01	1075	Six months of physiotherapy following discharge	6	47	2759
22.29	461	12 months of physiotherapy following discharge	9	23	4139
0.11	2	Only admitted for rehabilitation	1.5	82	690
0.36	7	Stay in convalescent unit following stay in stroke unit (mean 44 days)	1.47	82	674
0.36	7	Stay in medium-term rehabilitation unit following discharge (mean 92 days)	3.1	70	1410
Diagnosed in previous years					
11.76	1905	No return to work	12	0	5518
23.47	1268[a]	Chronic rehabilitation for three months	1.57	49	720
64.77	13 028	Able to return to work	0	56	0

[a] It is assumed that only a third of patients undergo chronic rehabilitation.

Indirect costs

Indirect costs of atrial fibrillation without stroke. When estimating the indirect costs of AF without stroke it was assumed that the disease's impact is only in terms of absenteeism, without early retirement.

Table 4 shows the estimates of number of working days lost per year for each disease due to consultations, exams, hospitalizations and convalescence. Length of hospital stay was estimated on the basis of DRGs. It was assumed that convalescence time for AF was equal to length of hospitalization. The employment rate of AF patients (low given the fact that many are past retirement age) was taken into account when calculating mean costs.

The costs of consultations and exams for patients in the first year of diagnosis were calculated by multiplying the mean costs in the first year by the number of patients in the first year of diagnosis (incidence), while the costs for patients diagnosed in previous years were obtained by multiplying the mean costs in subsequent years by the prevalence (minus incidence). Finally, the total indirect costs arising from hospitalizations due to AF were calculated by multiplying the indirect costs of days spent in hospital and convalescing by the number of admissions. Adding these estimates together, we arrive at a total indirect cost of AF without stroke of €6.77 million.

Indirect costs of atrial fibrillation with stroke. Estimating the indirect costs of AF with stroke is more complicated, since there are different subgroups of patients depending on the consequences of the stroke and the need for rehabilitation after the event. The findings of the expert panel were used to identify possible scenarios following stroke and the proportion of patients in each scenario, each of which involves different levels of absenteeism resulting from physiotherapy sessions and differences in ability to return to work. Table 5 summarizes the possible scenarios, the number of patients in each scenario, and the indirect costs per patient with AF and ischemic stroke for the population initially employed.

According to the expert panel, 12% of patients who suffer stroke attributable to AF are unable to return to work, 52% need six months of physiotherapy after hospitalization and 22% need 12 months, leading to absenteeism of six and nine months, respectively, assuming that after six months of physiotherapy the patient loses half a working day for each physiotherapy session for the following six months.

The expert panel also calculated that only 0.83% of patients with stroke attributable to AF are unable to work for a period of less than three months. As for those with AF-related stroke AF in previous years, 12% have still not returned to work, while 23% are absent from work for the equivalent of one and a half months a year.

The estimates in Table 6 show that the indirect costs of ischemic stroke attributable to AF amount to almost €20 million. Thus, considering all aspects of the indirect costs of ischemic stroke, the total indirect costs attributable to AF are calculated to be €25 million.

Table 6 Indirect costs of stroke attributable to atrial fibrillation.

	Consultations		Exams		Rehabilitation		Hospitalization and convalescence
	Year of diagnosis	Patients diagnosed in previous years	Year of diagnosis	Patients diagnosed in previous years	Year of diagnosis	Patients diagnosed in previous years	Year of diagnosis
No. of working days lost	2.74	1.56	1.17	0.8			22.6
Cost per patient (€)	66	37	28	19			542
Total annual indirect costs (€)	64 656	171 192	27 593	86 559	6 549 699	11 352 054	153 999
Total (€)							18 405 752

AF: atrial fibrillation.

Discussion

AF is the most common sustained arrhythmia in Portugal. According to the FAMA study, its prevalence in 2009 was 2.5%

in the population aged 40 and over and more than 10% in those aged 80 and over; only 60% of cases were diagnosed. As in other countries, the prevalence of AF in Portugal is increasing, probably due to aging populations and better diagnosis. As an example of this trend, there were 4678 admissions with a primary diagnosis of AF in NHS hospitals in Portugal in 2008, while the corresponding figure for 2012 was 6765, an increase of 45%.

The main purpose of this study is to provide an estimate of the burden of disease in terms of DALYs and costs to society. The results are a clear statement of the seriousness of AF in Portugal. Stroke is highly disabling and frequently results in early retirement; as well as the costs involved, the burden of AF reflects the fact that stroke in AF patients is particularly lethal and, for those who survive, disabling.

For methodological reasons, the figures presented in this study underestimate the cost and burden of the disease, since they do not consider bleeding episodes, including intracranial hemorrhage, a major complication of the anticoagulant therapy used as prophylaxis against stroke in AF patients.

Conclusions

This analysis shows that 4070 deaths can be attributed to AF in 2010 in Portugal, corresponding to 3.8% of all deaths, and that the total burden of disease attributable to AF is 23 084 DALYs. The overall cost of illness is estimated at €140.7 million, around 0.08% of Portugal's gross domestic product. These figures confirm the importance of AF, but at the same time they make it clear that this is an area in which significant health gains can be made.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors have no conflicts of interest to declare.

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ARTIGO ORIGINAL

Custo-efetividade dos novos anticoagulantes orais na fibrilhação auricular em Portugal

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PALAVRAS-CHAVE
Anticoagulantes orais;
Fibrilhação auricular;
Custo-efetividade;
Anos de vida ajustados pela qualidade

Resumo
Introdução e objetivos: Os *non-vitamin K antagonist oral anticoagulants* (NOAC) foram recentemente comparticipados para a fibrilhação auricular não-valvular (FA), sendo relevante determinar o seu custo-efetividade para a realidade portuguesa.
Métodos: Foi especificado um modelo Markov para simular a progressão dos doentes com FA no decurso da sua vida. Os dados de efetividade relativa para os eventos acidente vascular cerebral (isquémico e hemorrágico), hemorragia (intracraniana, outras hemorragias *major* e hemorragias *não-major* clinicamente relevantes), enfarte agudo do miocárdio e descontinuação do tratamento foram obtidos por comparações indiretas entre o apixabano, o dabigatrano e o rivaroxabano (comparador comum: varfarina). As fontes dos dados de consumo de recursos de saúde foram a base de dados dos grupos de diagnóstico homogéneo e painel de peritos. Estimou-se os anos de vida ganhos, anos de vida ajustados pela qualidade (QALY), custos diretos e rácios de custo-efetividade incremental (ICER).
Resultados: Os anos de vida ganhos e os QALY foram maiores com apixabano, com um ICER *versus* varfarina e dabigatrano de 5529 € / QALY e 9163 € / QALY, respetivamente. O apixabano foi dominante *versus* o rivaroxabano (maiores ganhos em saúde e menores custos). Estes resultados foram robustos nas análises de sensibilidade realizadas, tendo o apixabano uma probabilidade de 70% de ser custo-efetivo (*threshold*: 20 000 € / QALY) *versus* o conjunto das restantes opções terapêuticas.

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Conclusões: A utilização de apixabano em doentes com FA na prática clínica portuguesa é custo-efetiva *versus* varfarina e dabigatrano e dominante *versus* rivaroxabano na perspetiva do SNS. Estas conclusões baseiam-se em comparações indiretas. Apesar desta limitação, esta informação é relevante para os diferentes decisores em saúde.

KEYWORDS
Oral anticoagulants;
Atrial fibrillation;
Cost-effectiveness;
Quality-adjusted life years

Cost-effectiveness of non-vitamin K antagonist oral anticoagulants for atrial fibrillation in Portugal

Abstract
Introduction and Objectives: Recently, three novel non-vitamin K antagonist oral anticoagulants received approval for reimbursement in Portugal for patients with non-valvular atrial fibrillation (AF). It is therefore important to evaluate the relative cost-effectiveness of these new oral anticoagulants in Portuguese AF patients.
Methods: A Markov model was used to analyze disease progression over a lifetime horizon. Relative efficacy data for stroke (ischemic and hemorrhagic), bleeding (intracranial, other major bleeding and clinically relevant non-major bleeding), myocardial infarction and treatment discontinuation were obtained by pairwise indirect comparisons between apixaban, dabigatran and rivaroxaban using warfarin as a common comparator. Data on resource use were obtained from the database of diagnosis-related groups and an expert panel. Model outputs included life years gained, quality-adjusted life years (QALYs), direct healthcare costs and incremental cost-effectiveness ratios (ICERs).
Results: Apixaban provided the most life years gained and QALYs. The ICERs of apixaban compared to warfarin and dabigatran were €5529/QALY and €9163/QALY, respectively. Apixaban was dominant over rivaroxaban (greater health gains and lower costs). The results were robust over a wide range of inputs in sensitivity analyses. Apixaban had a 70% probability of being cost-effective (at a threshold of €20 000/QALY) compared to all the other therapeutic options.
Conclusions: Apixaban is a cost-effective alternative to warfarin and dabigatran and is dominant over rivaroxaban in AF patients from the perspective of the Portuguese national healthcare system. These conclusions are based on indirect comparisons, but despite this limitation, the information is useful for healthcare decision-makers.

Glossário de abreviaturas

95% IC	Intervalo de Confiança a 95%
AVC	Acidente Vascular Cerebral
CHLC	Centro Hospitalar Lisboa Central, EPE
cTTR	*Center's median time in therapeutic range*
CV	Cardiovascular
EAM	Enfarte Agudo do Miocárdio
ES	Embolismo Sistémico
FA	Fibrilhação Auricular não-valvular
GDHs	Grupos de Diagnóstico Homogéneos
GI	Gastrointestinal
HCR(NM)	Hemorragias Clinicamente Relevantes (Não-*Major*)
HFF	Hospital Fernando da Fonseca, EPE
HIC	Hemorragia Intracraniana
HM	Hemorragias *Major*
HR	*Hazard Ratio*
IC	Intracraniana
ICER	*Incremental cost-effectiveness ratio*
INE	Instituto Nacional de Estatística
INR	Rácio normalizado internacional - *International normalized ratio*
ITC	Comparação indireta frequencista - *Indirect treatment comparison*
MCDTs	Meios complementares de diagnóstico e terapêutica
mRS	Escala Rankin modificada
NMA	*Network Meta-Analysis*
NOACS	*Non-Vitamin K Antagonist Oral Anticoagulants*
OR	*Odds Ratio*
PTAT	Proporção de Tempo no Alvo Terapêutico
QALYs	*Quality-Adjusted Life Years*
RR	Risco Relativo
SNS	Serviço Nacional de Saúde

List of Abbreviations

95% CI	95% Confidence Interval
AVC	Stroke
CHLC	Centro Hospitalar Lisboa Central, EPE
cTTR	Center's median time in therapeutic range
CV	Cardiovascular
EAM	Acute Myocardial Infarction
ES	Systemic Embolism
FA	Non valvular atrial fibrillation
GDHs	Diagnosis Related Groups
GI	Gastrointestinal
HCR(NM)	Clinically Relevant Non-Major Bleeding
HFF	Hospital Fernando da Fonseca, EPE
HIC	Intracranial Bleeding
HM	Major Bleeding
HR	Hazard Ratio
IC	Intracranial
ICER	Incremental cost-effectiveness ratio
INE	National Institute of Statistics
INR	International normalized ratio
ITC	Indirect Treatment Comparison
MCDTs	Complementary means of diagnosis and therapeutic
mRS	Modified Rankin scale
NMA	Network Meta-Analysis
NOACS	Non-Vitamin K Antagonist Oral Anticoagulants
OR	Odds Ratio
PTAT	Time proportion within therapeutic range
QALYs	Quality-Adjusted Life Years
RR	Relative Risk
SNS	National Health Service

Introdução

A fibrilhação auricular (FA) é a arritmia persistente mais prevalente na prática clínica. Em Portugal estima-se que 2,5% dos indivíduos com mais de 40 anos tenham FA, sendo a prevalência superior a 10% nos indivíduos com mais de 80 anos[1]. Uma vez que a FA pode ser assintomática e permanecer sem diagnóstico até que ocorra uma complicação (acidente vascular cerebral [AVC] isquémico ou embolia periférica sistémica)[2,3], está atualmente recomendado o seu rastreio clínico em todos os doentes com mais de 65 anos. O conhecimento desta condição é essencial para estratificar o risco tromboembólico e decidir sobre a instituição de medicação profilática das complicações tromboembólicas associadas. A anticoagulação oral com antagonistas da vitamina K é a principal intervenção farmacológica utilizada com este objetivo, estando associada a uma redução superior a 50% do risco de AVC em doentes com FA[4]. Apesar da eficácia verificada em ensaios clínicos, a utilização destes fármacos tem sido consistentemente reportada como subótima[5].

Mais recentemente, surgiram novas opções farmacológicas com os mesmos objetivos terapêuticos, nomeadamente os designados novos anticoagulantes orais – *non-vitamin K antagonist oral anticoagulants* (NOAC). A sua eficácia é considerada, pelo menos, similar aos antagonistas da vitamina K[6], com menor risco de hemorragia intracraniana[7] e sem necessidade de controlo laboratorial da hemostase do *international normalized ratio* (INR). Até à data, foram comparticipados para a FA em Portugal três destes NOAC: apixabano, dabigatrano e rivaroxabano. Estes fármacos são distintos, com mecanismos de ação, características farmacocinéticas e regimes posológicos diferentes que influenciam a opção terapêutica entre eles perante o doente individual, como sejam o grau de disfunção renal, a idade, o risco hemorrágico, a história prévia de doença coronária ou arterial periférica e o risco de AVC.

Apesar do impacto orçamental associado a estes novos medicamentos, os estudos já publicados sobre o custo-efetividade de dabigatrano e rivaroxabano *versus* varfarina na FA para a realidade portuguesa indicam que a utilização destas intervenções na prática clínica portuguesa é custo-efetiva[8,9]. Desde um de agosto de 2014, estes NOAC foram comparticipados pelo Serviço Nacional de Saúde (SNS) para a prevenção de eventos tromboembólicos em doentes com FA não-valvular. Neste contexto, é relevante, para os diferentes decisores, conhecer os ganhos em saúde e os custos associados aos diferentes NOAC. O objetivo deste trabalho foi, portanto, estimar o custo-efetividade dos NOAC, em particular do apixabano (o mais recente NOAC a obter autorização de introdução no mercado) comparativamente a varfarina, dabigatrano e rivaroxabano.

Métodos

Estrutura do modelo

O modelo de custo-efetividade e custo-utilidade é um modelo de Markov, com ciclos de seis semanas (duração mínima expectável em que pode ocorrer alteração dos sintomas ou da patologia) que segue uma coorte de 1000 doentes no horizonte temporal coincidente com o tempo de vida (*lifetime*). O modelo é programado em *Excel* com *Visual Basic for Applications* (Figura 1) e os seus detalhes foram recentemente (2014) publicados por Lip et al.[10].

No modelo, a história natural da doença foi representada de forma simplificada em 11 estadios de saúde mutuamente exclusivos: FA não-valvular; AVC isquémico não-fatal ligeiro, moderado e grave; AVC hemorrágico não-fatal ligeiro, moderado e grave; embolismo sistémico (ES); enfarte agudo do miocárdio (EAM); FA não-valvular em que foi descontinuada a anticoagulação inicial; e morte. Após um intervalo de seis semanas, um doente poderá transitar para outro estádio de acordo com a respetiva probabilidade de transição. A cada estádio está associada uma probabilidade de ocorrer um evento no intervalo de tempo considerado. O risco de AVC isquémico depende do *score* $CHADS_2$[11] – modelo de estratificação de risco tromboembólico utilizado à data da realização dos ensaios clínicos – e do nível de adequabilidade da hipocoagulação para os doentes tratados com varfarina, determinado pela mediana do tempo em que os valores do INR se encontram dentro do intervalo terapêutico. As probabilidades de ocorrência de AVC, EAM, outras hemorragias intracranianas e outras hemorragias *major* e *não-major* aumentam com a idade, refletindo o risco acrescido de ocorrência destes eventos ao longo da vida. O modelo considera também o impacto a longo prazo do EAM e do ES na mortalidade (*hazard ratio* [HR] mais altos).

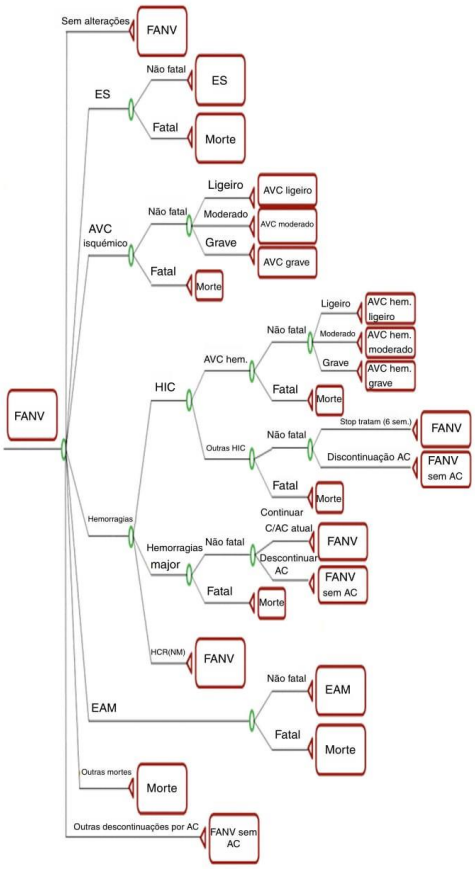

Figura 1 Modelo de Markov: árvore de decisão.
AC: anticoagulantes; AVC: acidente vascular cerebral; EAM: enfarte agudo do miocárdio; ES: embolismo sistémico; FANV: fibrilhação auricular não valvular; FANV sem AC: fibrilhação auricular não valvular; HCR (NM): hemorragias clinicamente relevantes (não-*major*); HIC: hemorragia intracraniana. Reproduzido de Lip et al.[10].

Caso o doente se encontre no estádio FA não-valvular, em que se suspendeu a anticoagulação inicial, a estrutura do modelo não se altera, mas as probabilidades de transição variam.

No cenário de ocorrência de um AVC (isquémico ou hemorrágico), a distribuição da gravidade do AVC é feita segundo a escala Rankin modificada (mRS)[12]: AVC não-fatal ligeiro (mRS: 0-2), moderado (mRS: 3-4) ou grave (mRS: 5) e AVC fatal (mRS: 6). Todos os doentes com AVC fatal transitam para o estádio morte no ciclo seguinte, enquanto os AVC não-fatais estão modelizados como um estádio «túnel», ou seja, estes doentes podem apenas ter uma recorrência de AVC ou morrer. O modelo permite que cada doente tenha apenas um AVC recorrente. Neste caso, o doente transita para o estádio correspondente ao AVC com gravidade igual ou superior ao primeiro AVC. O modelo não considera possível a recorrência de EAM ou de ES. Nestes casos, o doente poderá apenas manter-se nesse estádio ou transitar para o estádio morte.

No final de cada intervalo são estimados os custos da doença, os anos de vida ajustados pela qualidade (*quality-adjusted life years* [QALY]) e os anos de vida acrescidos. Os níveis de qualidade de vida relacionada com a saúde (utilidades), *outcomes* clínicos e as taxas de mortalidade variam consoante o grau de gravidade do AVC. Conforme estipulado nas Orientações Metodológicas para Estudos de Avaliação Económica de Medicamentos do Infarmed[13], os custos e efetividades foram atualizados à taxa de 5%.

População

No cenário base, a população considerada no modelo corresponde às características dos doentes incluídos nos ensaios com apixabano, mais concretamente no ensaio ARISTOTLE[14], em termos de idade média (70 anos), género (64,7% homens) e distribuição dos *scores* $CHADS_2$ (*score* 1-2: 69%; *score* 3-4: 27% e *score* 5-6: 4%).

Comparadores

Neste estudo, os resultados do tratamento com apixabano 2,5-5 mg, duas vezes por dia, são comparados aos resultados obtidos com: 1) dabigatrano, na dose de 150 mg até os 80 anos e na dose de 110 mg após os 80 anos, em doentes com risco hemorrágico elevado e nos tratados com verapamilo, ambas dosagens duas vezes por dia. Este grupo será designado como dabigatrano; 2) rivaroxabano 15-20 mg, uma vez por dia.

Efetividade relativa dos *non-vitamin K antagonist oral anticoagulants*: comparações indiretas

Os estudos de avaliação económica de novas tecnologias em saúde (por exemplo, medicamentos) dependem da efetividade dessas tecnologias e dos custos associados às mesmas, comparativamente às opções existentes. Neste contexto, a estimativa da efetividade relativa dos NOAC é um dos aspetos centrais neste estudo. Até à data, não existem comparações diretas entre os NOAC (ensaios *head-to-head*), pelo que as efetividades na FA têm de ser estimadas com análise de comparação indireta, utilizando um comparador comum (neste caso, a varfarina).

Neste contexto, torna-se fundamental avaliar a consistência das estimativas da efetividade utilizadas no modelo económico. Para tal, realizámos uma revisão sistemática da literatura para identificar as comparações indiretas publicadas entre os NOAC que disponibilizassem dados de efetividade relativa na FA. Utilizámos os termos *meta-analysis, indirect comparison, bayesian, network, apixaban, dabigatran, rivaroxaban e atrial fibrillation*, nas bases de dados MEDLINE e *Cochrane Library* (setembro de 2014). Identificámos dez comparações indiretas: seis do tipo frequencista[10,15–19] e quatro do tipo *bayesiano* (meta-análises em rede)[6,20–22].

Tabela 1 Características das comparações indiretas publicadas entre os NOAC na FA

Estudos	Medida de associação	Ensaios clínicos incluídos
Comparações indiretas frequencistas		
Lip et al.[10], 2014	HR	RE-LY, ROCKET AF, ARISTOTLE
Testa et al.[17], 2012	OR	RE-LY, ROCKET AF, ARISTOTLE
Harenberg et al.[16], 2012	OR	RE-LY, ROCKET AF, ARISTOTLE
Baker et al.[15], 2012	RR	RE-LY, ROCKET AF, ARISTOTLE, PETRO
Lip et al.[18], 2012	HR	RE-LY, ROCKET AF, ARISTOTLE
Meta-análise em rede (bayesiano)		
Mitchell et al.[20], 2013	HR	RE-LY, ROCKET AF, ARISTOTLE
Assiri et al.[22], 2013	RR	RE-LY, ROCKET AF, ARISTOTLE, 18 outros RCT
Dogliotti et al.[6], 2014	OR	RE-LY, ROCKET AF, ARISTOTLE, AVERROES, ACTIVE-W, ACTIVE-A11 comparações *versus* placebo
Cameron et al.[21], 2014	OR	RE-LY, ROCKET AF, ARISTOTLE, ARISTOTLE J, ENGAGE AF AVERROES, ACTIVE-W, ACTIVE-A comparações *versus* placebo

HR: *hazard ratio*; OR: *odds ratio*; RR: risco relativo.

A Tabela 1 mostra as características sumárias de cada uma destas comparações indiretas. Conforme se pode verificar na Figura 2, as estimativas destas publicações para os vários resultados (*outcomes*) que o modelo considera são consistentes entre si e semelhantes às utilizadas no caso base no modelo económico (Lip et al.[10]). Dado o objetivo do presente estudo, os dados reportados por Lip et al.[10] (comparação indireta frequencista pelo método de Bucher[23]) e por Mitchell et al.[20] (meta-análise em rede do tipo bayesiano) correspondem provavelmente às melhores estimativas das efetividades relativas entre os três NOAC na FA, por utilizarem apenas os dados dos ensaios clínicos de fase III destes NOAC e por estabelecerem associações utilizando o HR, que tem em conta o fator temporal e respeita a análise estatística primária de cada ensaio. A Figura 3; Suplementar (Anexo) mostra a rede de evidência utilizada por estas duas comparações indiretas.

Efetividade relativa dos *non-vitamin K antagonist oral anticoagulants*: taxas de eventos

As taxas de eventos consideradas no cenário base do modelo são aquelas resultantes dos HR reportadas por Lip et al.[10] (Tabela 2). A distribuição dos eventos de AVC por gravidade é apresentada no Anexo (Tabela 3; Suplementar).

Como mencionado anteriormente, o risco de AVC isquémico e de eventos hemorrágicos associados ao uso de varfarina depende do nível de adequabilidade da hipocoagulação (controlo dos valores de INR) (Tabela 4; Suplementar). O modelo distribui os doentes em quatro categorias, de acordo com vários *cut-offs* para o *center's median time in therapeutic range* (cTTR), conforme resultados obtidos nos vários centros que participaram no ensaio ARISTOTLE. Esta distribuição é uniforme, ou seja, 25% dos doentes em cada categoria.

Tabela 2 *Hazard ratios* (IC 95%): apixabano *versus* varfarina e outros NOAC

	Apixabano	Varfarina	Dabigatrano 110 mg	Dabigatrano 150 mg	Rivaroxabano
AVC isquémico	1,00	1,09 (0,89; 1,35)	1,20 (0,88; 1,64)	0,82 (0,60; 1,14)	0,98 (0,72; 1,33)
Hemorragia intracraniana[a]	1,00	2,38 (1,72; 3,33)	0,73 (0,43; 1,26)	1,02 (0,62; 1,68)	1,73 (1,08; 2,77)
ES	1,00	1,00 (0,90; 1,10)[b]	1,00 (0,90; 1,10)[b]	1,00 (0,90; 1,10)[b]	1,00 (0,90; 1,10)[b]
Outras hemorragias *major*	1,00	1,27 (1,08; 1,47)	1,21 (0,97; 1,50)	1,37 (1,10; 1,71)	1,44 (1,15; 1,79)
Hemorragias clinicamente relevantes (não-*major*)	1,00	1,43 (1,24; 1,66)	1,16 (0,99; 1,35)	1,30 (1,11; 1,53)	1,49 (1,26; 1,76)
EAM	1,00	1,14 (0,86; 1,52)	1,47 (0,96; 2,27)	1,46 (0,95; 2,24)	0,94 (0,64; 1,38)
Outras hospitalizações CV	1,00	1,00 (0,90; 1,10)[c]	1,00 (0,90; 1,10)[c]	1,00 (0,90; 1,10)[c]	1,00 (0,90; 1,10)[c]

[a] A hemorragia intracraniana inclui o AVC hemorrágico e outros tipos de hemorragias intracranianas. A proporção de AVC hemorrágico foi de 77, 64, 64, 41 e 57% para apixabano, varfarina, dabigatrano 110 mg, dabigatrano 150 mg e rivaroxabano, respetivamente, de acordo com a literatura (análise secundária do estudo ARISTOTLE; RE-LY; ROCKET AF).

[b] Pressuposto, dada a reduzida taxa de eventos de ES nos ensaios.

[c] Assume-se igual à apixabano.

AVC: acidente vascular cerebral; EAM: enfarte agudo do miocárdio; ES: embolismo sistémico.

Fonte: Lip et al.[10], 2014.

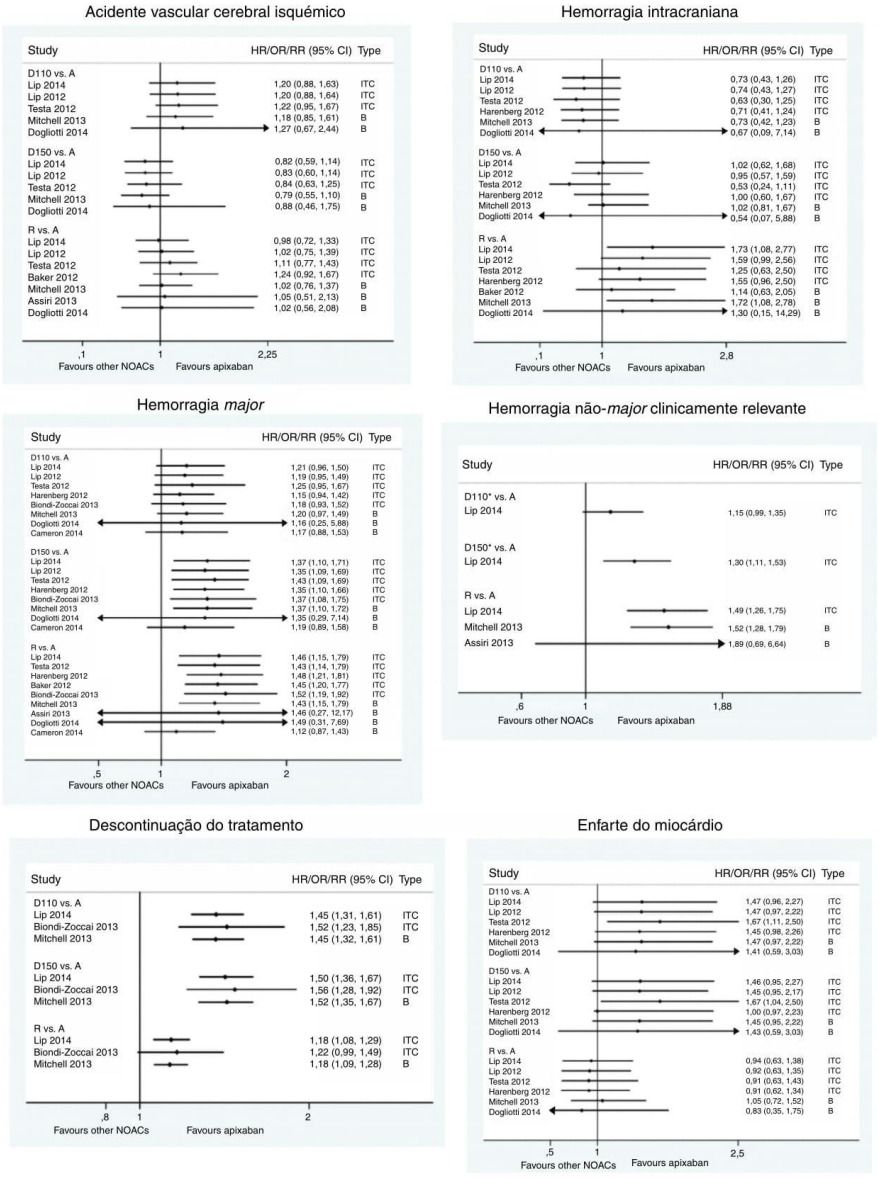

Figura 2 Estimativas de efetividade do apixabano *versus* outros NOAC nas comparações indiretas publicadas.
A: apixabano; B: meta-análise em rede bayesiana; D: dabigatrano; ITC: comparação indireta frequencista; R: rivaroxabano. *O estudo RE-LY apresenta apenas resultados para hemoragias *minor*, que foram utilizadas como *proxy* de hemorragias clinicamente relevantes (não-*major*).

Para parametrizar o modelo de acordo com a realidade portuguesa, em termos do nível de adequabilidade da hipocoagulação, utilizámos os dados de uma amostra de conveniência proveniente da Consulta de Hipocoagulação do Centro Hospitalar Lisboa Central, EPE (CHLC) e do Hospital Fernando da Fonseca, EPE (HFF). Estes dados referem-se ao período entre 2011-2012 e incluem todos os doentes com, pelo menos, dez registos de INR, no total 39 630 medições de INR respeitantes a 2850 doentes. Com base nestes dados, foi calculada a mediana da proporção de tempo em que os valores de INR de um doente se encontravam no alvo terapêutico (proporção de tempo no alvo terapêutico [PTAT]). Dado que a informação é limitada a dois hospitais, não é possível estimar a mediana do tempo no alvo terapêutico de vários centros (cTTR), mas apenas a mediana da PTAT dos doentes avaliados nestes dois hospitais. Esta medida foi considerada uma aproximação do cTTR definido no modelo. A robustez dos resultados obtidos a partir desta amostra de base hospitalar foi verificada contra uma amostra com avaliações de INR em unidades de base ambulatória, que incluiu 4470 medições de INR respeitantes a 233 doentes, não tendo sido detetadas diferenças estatisticamente significativas.

Com base nestes dados, verifica-se que o nível de adequabilidade da hipocoagulação na amostra portuguesa é inferior à considerada no modelo, uma vez que 44,5% dos doentes portugueses têm uma PTAT $\geq$ 52,38% e no modelo é considerado que 75% dos doentes tinham um cTTR $\geq$ 52,38% (Tabela 5; Suplementar).

As taxas de descontinuação de tratamento por 100 pessoas/ano devido a causas não vasculares foram obtidas a partir de uma análise secundária dos dados do ensaio ARISTOTLE (13,2% com apixabano e 14,4% com varfarina). Assumiu-se que as taxas foram constantes ao longo do tempo. A Tabela 6; Suplementar mostra os HR de descontinuação de tratamento por causas não devidas aos eventos vasculares. A segunda linha de tratamento considerada foi ácido acetilsalicílico. Os riscos absolutos associados aos eventos por 100 pessoas/ano são resumidos na Tabela 7; Suplementar.

Custos

O estudo adota a perspetiva do SNS. Por conseguinte, não estão incluídos na análise os custos indiretos. Deste modo, o modelo identifica três fontes principais de custos: custos gerados pela ocorrência dos eventos vasculares, custos da terapêutica anticoagulante e custos das consultas de monitorização e/ou de rotina. O custeio baseou-se: 1) na Portaria n.º 20/2014 de 29 de janeiro[24] para efeitos dos preços unitários das consultas, dos meios complementares de diagnóstico e terapêutica (MCDT) e dos grupos de diagnóstico homogéneos (GDH); 2) na análise da base de dados dos internamentos (GDH) no SNS em 2013[25]; 3) na base de dados de medicamentos do Infarmed (Infomed), que disponibiliza informação relativa aos preços dos medicamentos (consultada em dois de janeiro de 2015)[26]; e 4) nos resultados da consulta de um painel de peritos de várias especialidades com representatividade geográfica, que estimaram os consumos de recursos de saúde em ambulatório. Para os estádios de saúde AVC isquémico e hemorrágico não-fatais, EAM e ES, os custos foram estimados distinguindo duas fases: aguda e de manutenção a longo prazo. Os consumos imputados à fase aguda incluem as duas primeiras semanas de internamento e a reabilitação ao longo dos primeiros três meses. O modelo assume que a fase de manutenção dura até à morte. De acordo com o painel de peritos, a fase de manutenção inclui custos associados a consultas, episódios de urgência e deslocações, MCDT, medicação e ajudas técnicas. Não foi possível estimar de forma consistente o custo dos AVC em função da sua gravidade (ligeiro, moderado e grave), uma vez que não existem dados de custo por mRS em Portugal. Para os restantes estádios de saúde foram imputados apenas os custos de internamento (fase aguda).

Os resultados dos custos globais por evento, dos custos da terapêutica e dos custos de monitorização e rotina são reportados na Tabela 8.

Mortalidade

As probabilidades de morte associadas aos eventos vasculares considerados no modelo foram aquelas observadas nos ensaios, com exceção da taxa de letalidade do EAM, a qual foi obtida a partir de Scarborough et al.[27]. O modelo assume que estas probabilidades são independentes do tratamento. Para o período que corresponde à duração do ensaio ARISTOTLE, a taxa de mortalidade por outras causas, que não pelos eventos vasculares considerados no modelo, assumiu-se igual para todos os NOAC, utilizando-se o valor do ensaio ARISTOTLE (3,08% para o apixabano e 3,34% para a varfarina). A mortalidade após o período avaliado nos ensaios clínicos foi modelizada com base nas tábuas de mortalidade portuguesas[28] e multiplicada pelo HR associado à população com FA estimado por Friberg et al. com o objetivo de ter em conta o risco acrescido da população considerada[29]. Em particular, foram estimados os parâmetros duma função de sobrevivência Gompertz por faixa etária (< 75 anos ou $\geq$ 75 anos) e por sexo. O modelo considera fatores de ajustamento do risco de mortalidade para incluir na análise os aumentos das taxas de mortalidade associadas à FA e AVC por grau de gravidade (Tabela 9; Suplementar).

Ponderadores de qualidade de vida relacionada com a saúde – utilidades

Os valores médios de utilidade da população e os decrementos associados aos vários estádios da doença foram considerados iguais aos valores britânicos estimados por Sullivan et al.[30] Existem também decrementos de utilidade associados à terapêutica com varfarina[31] (contrariamente à terapêutica com NOAC) e à ocorrência de outros eventos vasculares. O modelo assume que estes decrementos podem ser aplicados aditivamente. A Tabela 10 resume as utilidades consideradas e os seus decrementos.

Análise de sensibilidade

Foram realizadas análises de sensibilidade univariadas para verificar a robustez dos resultados em relação aos seguintes parâmetros: 1) utilização dos HR estimados por Mitchell

Tabela 8 Custos gerados pela ocorrência dos eventos vasculares, terapêutica anticoagulante e consultas de rotina/monitorização

	Custos	
Eventos	Agudos (por episódio)	Longo prazo (por mês)
AVC isquémico não fatal (média ponderada)	8653,26 €	44,57 €
AVC isquémico fatal	6381,20 €	-
AVC hemorrágico não fatal (média ponderada)	13 779,62 €	41,07 €
AVC hemorrágico fatal	10 419,64 €	
Outras hemorragias intracranianas	7932,21 €	-
Hemorragias GI	2798,64 €	-
Hemorragias não-IC e não-GI	2090,04 €	-
Hemorragias clinicamente relevantes não-*major*	2514,98 €	42,32 €
ES	3937,93 €	-
EAM	4560,10 €	53,61 €
Outros internamentos por evento cardiovascular	2081,64 €	-

		Consulta de rotina/monitorização	
Medicação	Custo médio diário*	Frequência mensal	Valor[b]
Varfarina	0,08 €	0,92[a]	31,00 €
Apixabano	2,41 €	0,33[c]	31,00 €
Dabigatrano 110 mg	2,36 €	0,33[c]	31,00 €
Dabigatrano 150 mg	2,46 €	0,33[c]	31,00 €
Rivaroxabano	2,47 €	0,33[c]	31,00 €

AVC: acidente vascular cerebral; CHLC: Centro Hospitalar Lisboa Central, EPE; EAM: enfarte agudo do miocárdio; ES: embolismo sistémico; IC: intracranianas; GI: gastrointestinais; HFF: Hospital Fernando da Fonseca, EPE.
Fonte: [a] base de dados CHLC e HFF; [b] Portaria GDH 20/2014[24]; [c] painel de peritos.
* Os preços dos medicamentos foram valorizados sem IVA.

et al.[20] (meta-análise em rede do tipo *bayesiano*), em vez dos estimados por Lip et al.[10]; 2) níveis de adequabilidade do controlo de hipocoagulação como verificado nos ensaios, em vez dos valores obtidos em doentes portugueses; 3) duração da fase aguda dos episódios de internamento de seis semanas, em vez de duas semanas; 4) custos de AVC diferentes dependentes do seu nível de gravidade com ponderação calculada a partir das estimativas

Tabela 10 Utilidades médias da população considerada no modelo e os seus decrementos

Utilidade considerada no modelo para cada estadio da doença[a]	
FA (utilidade de base)	0,7270
AVC (isquémicos e hemorrágicos)	
Ligeiro	0,6151
Moderado	0,5646
Grave	0,5142
ES	0,6265
EAM	0,6098
Decremento da utilidade associado à terapêutica com anticoagulantes e à ocorrência de outros eventos vasculares (duração)	
Anticoagulantes	
Varfarina[b]	0,0130*
NOAC	0,0000*
Eventos	
Outras hemorragias intracranianas (excluindo AVC hemorrágico)	0,1511 (seis semanas)
Outras hemorragias *major* (excluindo hemorragias intracranianas)	0,1511 (14 dias)
Hemorragias não-*major* clinicamente relevantes	0,0582 (dois dias)
Outros internamentos CV	0,1276 (seis dias)

AVC: acidente vascular cerebral; CV: cardiovascular; EAM: enfarte agudo do miocárdio; ES: embolismo sistémico; FA: fibrilhação auricular; NOAC: *non-vitamin K antagonist oral anticoagulants*.
Fonte: [a] Sullivan et al.[30], 2011; [b] Gage et al.[31], 2006.
* Enquanto os doentes estão em tratamento com anticoagulantes.

inglesas, em vez do custo uniforme de AVC para qualquer nível de gravidade; 5) distribuição dos eventos de AVC por gravidade similar para todos os NOAC (assumindo a distribuição do apixabano); 6) taxas de descontinuação do tratamento por outras causas (que não pelos eventos vasculares) igual à do apixabano (13,2%/ano) para todos os comparadores desde o início do tratamento, em vez das taxas de descontinuação reportadas nos ensaios; 7) taxas de mortalidade após o período avaliado no ensaio, iguais às da população em geral, com consequente subestimativas das taxas de mortalidade; 8) utilização de diferentes utilidades associadas a cada estádio (como estimadas na publicação precedente de Sullivan et al.,[46] e utilizadas noutros estudos de custo-efetividade de NOAC[32–34]); 9) taxa de atualização de custos e utilidades (0 ou 3%, em vez de 5%).

Foi também realizada uma análise probabilística de sensibilidade, utilizando simulações de Monte-Carlo (2000 simulações) incorporando incerteza de segunda ordem[35]. Os resultados são apresentados como a probabilidade do apixabano ser custo-efetivo *versus* outras opções terapêuticas utilizando um *threshold* de 20 000 € por QALY, limiar habitualmente considerado como aceitável para o financiamento de novas tecnologias de saúde em Portugal.

Resultados

Taxa de eventos e custos

A Tabela 11 resume o número de eventos vasculares com cada anticoagulante numa coorte de 100 000 doentes

Tabela 11 Número de eventos em cada opção terapêutica (taxa por 100 000 doentes)

Número de eventos (população total)	Apixabano	Varfarina	Dabigatrano	Rivaroxabano
AVC isquémico				
Não fatal	19 799	20 703	20 066	19 649
Fatal	2932	2857	3392	3283
Total	22 731	23 560	23 458	22 931
AVC hemorrágico				
Não fatal	1602	2040	996	1879
Fatal	1007	2171	702	938
Total	2609	4212	1698	2818
ES				
Não fatal	2138	2175	2403	2263
Fatal	221	225	249	234
Total	2359	2400	2652	2497
Outras hemorragias IC				
Não fatal	1063	2255	1521	1901
Fatal	159	337	227	284
Total	1221	2591	1748	2185
Outras hemorragias major				
Hemorragias não fatais GI	5055	5713	7501	8338
Hemorragias não fatais não- IC e não GI	8137	10 123	8984	10 802
Fatal	269	326	336	391
Total	13 461	16 159	16 822	19 530
Hemorragias não-*major* clinicamente relevantes	25 248	30 700	29 914	33 367
EAM				
Não fatal	7179	7345	8366	7182
Fatal	1043	1067	1214	1044
Total	8222	8412	9579	8226
Outras hospitalizações CV	116 048	112 390	117 558	116 738
Outros motivos de descontinuação do tratamento	63 406	62 408	72 720	66 616
Óbitos				
Relacionados com o evento clínico (agudo)	5940	7332	6364	6480
Relacionados com o evento clínico (morte devida a AVC, EAM, embolismo sistémico)	30 524	32 066	31 694	30 779
Outros	63 536	60 602	61 942	62 741
Total	100 000	100 000	100 000	100 000

AVC: acidente vascular cerebral; CV: cardiovascular; EAM: enfarte agudo do miocárdio; ES: embolismo sistémico; IC: intracranianas; GI: gastrointestinais.

Tabela 12 Custo total médio por doente, com cada opção terapêutica no horizonte temporal coincidente com o tempo de vida *(lifetime)*

Custos	Varfarina	Apixabano	Dabigatrano	Rivaroxabano
Eventos clínicos	5467,29 €	4989,03 €	5244,03 €	5386,30 €
Terapêutica	214,42 €	3754,35 €	3015,69 €	3463,96 €
Monitorização e cuidados de rotina	3252,29 €	1254,77 €	1311,27 €	1278,31 €
Total	8934,16 €	9998,14 €	9570,99 €	10 128,56 €

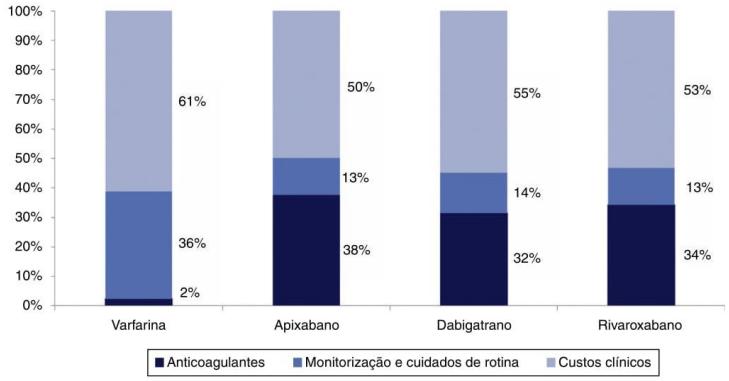

Figura 4 Estrutura do custo total médio por doente com cada opção terapêutica no horizonte temporal coincidente com o tempo de vida (*lifetime*).

conforme as taxas resultantes do modelo. De salientar que o número de eventos vasculares e óbitos relacionados com eventos clínicos é menor com apixabano, exceto no caso de AVC hemorrágico. Esta diferença no número de eventos *versus* as outras opções terapêuticas é de maior magnitude no caso do AVC isquémico, outras hemorragias *major*, hemorragias não-*major* clinicamente relevantes e óbitos relacionados com eventos clínicos.

A Tabela 12 e a Figura 4 resumem os custos associados às diferentes opções e a sua estrutura. A terapêutica com varfarina é a opção com menor custo total médio por doente e a terapêutica com rivaroxabano a mais dispendiosa. O custo total médio por doente com apixabano – considerando o horizonte temporal da análise (*lifetime*) – situa-se neste intervalo. O apixabano é a opção com menores custos clínicos (dado estar associado a uma menor taxa de eventos vasculares) e com menores custos relacionados com monitorização e cuidados de rotina. Os custos da terapêutica com apixabano ao longo da vida são maiores dada a maior duração de tratamento, a qual, por sua vez, é devida à menor descontinuação da terapêutica. Assim, apesar do custo diário do apixabano ser inferior ao de dabigatrano e

Tabela 13 Resultados de custo-efetividade no cenário de base: apixabano *versus* varfarina e outros NOAC

	Apixabano *versus*		
	Varfarina	Dabigatrano	Rivaroxabano
Custos incrementais	1063,98 €	427,15 €	−130,42 €
Anos de vida ganhos	0,19	0,05	0,04
QALY incrementais	0,19	0,05	0,03
ICER			
Custo por ano de vida ganho	5708,44 €	7926,91 €	Dominante
Custo por QALY ganho	5529,05 €	9162,77 €	Dominante

ICER: rácio de custo-efetividade incremental; QALY: quality-adjusted life years.

rivaroxabano, os custos da terapêutica com apixabano são maiores quando se considera o horizonte temporal coincidente com o tempo de vida.

Custo-efetividade de apixabano *versus* outras opções terapêuticas

A Tabela 13 e a Figura 5 mostram os resultados da análise de custo-efetividade de apixabano *versus* as outras opções terapêuticas. Como sugerido na literatura[36,37], no caso das comparações múltiplas, apresentam-se os resultados num gráfico onde as abcissas representam a diferença de QALY e as ordenadas a diferença de custo entre os comparadores e uma terapêutica de referência (*i.e.* varfarina). A linha vermelha que une os pontos do gráfico representa a fronteira de eficiência. A fronteira é caracterizada por três traços: a sua inclinação é de 4367 €/QALY quando une os pontos representantes da varfarina e de dabigatrano; de 9163 €/QALY quando une os pontos de dabigatrano e do apixabano, e é vertical a partir do apixabano porque não existe tecnologia mais efetiva. O rivaroxabano é dominado porque se encontra à esquerda da fronteira de custo-efetividade (apresentando mais custos e menos QALY que as combinações das alternativas terapêuticas na fronteira). O rivaroxabano é, aliás, dominado pelo apixabano considerado isoladamente.

Análise de sensibilidade

Os resultados da análise de sensibilidade univariada e probabilística suportam a robustez dos resultados obtidos. Na análise unidimensional para os nove parâmetros antes mencionados, e que refletem um conjunto de cenários alternativos, o apixabano é sempre dominante relativamente ao rivaroxabano. Comparativamente às restantes opções, em oito dos nove cenários considerados, o apixabano apresenta ICER muito inferiores a 20 000 €/QALY, variando entre 4909 e 6741 €/QALY *versus* varfarina e entre 5162 e 12 016 €/QALY *versus* dabigatrano. Quando se assume que as taxas de descontinuação por outras causas são iguais desde o início do tratamento, o apixabano induz custos menores relativamente ao rivaroxabano e ao dabigatrano. Neste cenário, o apixabano é dominante *versus* rivaroxabano e, para um *threshold* de 20 000 €/QALY, é custo-efetivo *versus* varfarina e dabigatrano. Os resultados das análises de sensibilidade são resumidos na Tabela 14; Suplementar).

No caso da análise de sensibilidade probabilística, a probabilidade do apixabano ser custo-efetivo, para um *threshold* de 20 000 €/QALY, é de 96, 87 e 95% *versus* varfarina, dabigatrano e rivaroxabano, respetivamente. Se todos os comparadores forem considerados simultaneamente (Figura 6), o apixabano é a melhor alternativa a partir de um *threshold* de 8000 €/QALY. Neste cenário, para uma disposição a pagar de 20 000 €/QALY, a probabilidade do apixabano ser custo-efetivo é de 70%.

Discussão

A FA é a arritmia cardíaca persistente mais prevalente[1] com um importante impacto social devido à mortalidade e morbilidade geradas, podendo atribuir-se à FA 3,8% do total

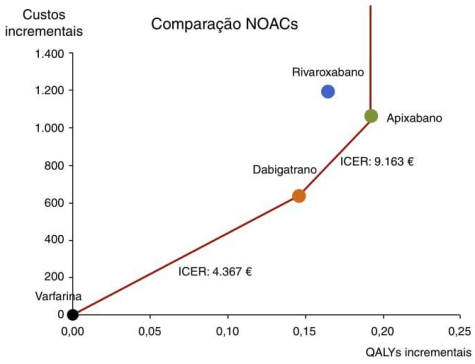

Figura 5 Efetividade (QALY) e custos incrementais dos NOAC relativamente à varfarina.
NOAC: non-vitamin K antagonist oral anticoagulants; QALY: quality-adjusted life years; ICER: incremental cost-effectiveness *ratio*.
Este gráfico compara a efetividade (QALY) e os custos incrementais dos NOAC relativamente à varfarina (representada na coordenada 0,0). A linha vermelha representa a fronteira de custo-efetividade. A sua inclinação em cada segmento corresponde ao ICER entre os pontos definindo esse segmento. Os NOAC com menos QALY incrementais localizam-se mais à esquerda e os NOAC com maiores custos incrementais localizam-se mais acima. O apixabano constitui uma opção terapêutica com custos incrementais de 1064 € face aos da varfarina, mas apresenta a maior efetividade comparativamente a todas as alternativas terapêuticas. Os pontos à esquerda da linha são dominados por combinações de terapêuticas mais efectivas que na fronteira. Neste caso, o rivaroxabano é estritamente dominado pelo apixabano, apresentando menos QALY e mais custos.

das mortes ocorridas em Portugal. Em termos de carga e custos da doença atribuível à FA para a realidade portuguesa, estima-se que esta seja responsável por cerca de 23 000 anos de vida perdidos ajustados pela incapacidade e por custos globais de cerca de 140 milhões de euros (M€), aproximadamente 0,08% do produto interno bruto[38]. É expectável que este cenário venha a assumir ainda maior importância no futuro, com o aumento da incidência e prevalência da FA devido ao envelhecimento da população e ao aumento da prevalência de doenças cardíacas crónicas, entre outros fatores[39]. Também o aumento do uso de monitorização eletrocardiográfica ambulatória, traduzindo-se em mais diagnósticos, contribui para que, neste contexto e no futuro, a FA constitua uma área onde se podem obter ganhos de saúde significativos.

A terapêutica antitrombótica, nomeadamente a anticoagulação, reduz significativamente o risco de eventos clínicos tromboembólicos relacionados com a FA, nomeadamente o de AVC[4]. Durante várias décadas, existiram poucas opções terapêuticas em termos de anticoagulação destes doentes, sendo a varfarina a terapêutica de referência. Mais recentemente, surgiram no mercado novos anticoagulantes (NOAC). Desde a sua comparticipação pelo SNS,

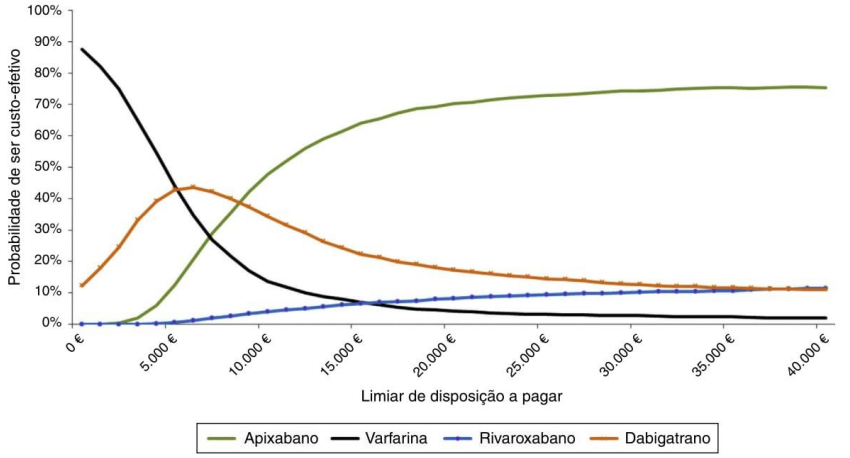

Figura 6 Curvas de aceitabilidade.
Este gráfico refere-se à curva de aceitabilidade, onde para cada valor da disposição a pagar se mostra a percentagem das simulações que são custo-efetivas para cada tratamento, permitindo uma comparação simultânea entre todas as opções terapêuticas. O apixabano é a melhor alternativa a partir dos 8000 €/QALY. Para uma disposição a pagar de 20 000 €/QALY, a probabilidade do apixabano ser custo-efetivo face ao conjunto de todas as alternativas é de 70%.

verificou-se um aumento muito significativo do número de doentes medicados com os NOAC, sendo expectável que a atual fração dos encargos do SNS com medicamentos de ambulatório atribuível aos anticoagulantes (4,5%, que corresponde a uma despesa estimada superior a 50 M€ em 2014) venha a aumentar[40]. Neste contexto, e com o intuito de informar os vários decisores em saúde, é relevante estimar o custo-efetividade relativo dos NOAC recentemente comparticipados para a prevenção do AVC na FA.

Foram publicados vários estudos de custo-efetividade onde cada um dos NOAC foi individualmente comparado com varfarina. Sem exceção, os resultados destes estudos, realizados em diferentes realidades, desde Europa aos EUA, mostraram que os NOAC são custo-efetivos *versus* varfarina[41]. No entanto, os resultados de custo-efetividade destes estudos não podem ser comparados de forma indireta e *naïve* para avaliar o custo-efetividade entre NOAC e, certamente, não refletem a realidade portuguesa. Neste contexto, realizámos um estudo de avaliação com base num modelo económico previamente publicado[10] que comparou os NOAC entre si, o qual foi parametrizado para a realidade portuguesa.

De acordo com os resultados do presente estudo, o apixabano é custo-efetivo *versus* varfarina e dabigatrano (ICER de 5529 €/QALY e 9163 €/QALY, respetivamente) e dominante *versus* rivaroxabano. A probabilidade de ser custo-efetivo, quando comparado simultaneamente com o conjunto das restantes alternativas terapêuticas, é de 70% considerando um *threshold* de 20 000 €/QALY. Estes resultados são concordantes com os de outros estudos para outras realidades europeias, como a Bélgica[42], a Holanda[32], o Reino Unido[10,43] e a França[44], em que o apixabano foi também custo-efetivo *versus* varfarina e custo-efetivo, ou mesmo dominante, *versus* dabigatrano e rivaroxabano. O facto do apixabano se apresentar como o NOAC mais custo-efetivo nestes estudos, deve-se possivelmente ao melhor perfil de efetividade do apixabano relativamente aos restantes NOAC, o qual poderá ser atribuível a um menor número de eventos vasculares comparativamente às restantes opções terapêuticas, nomeadamente de AVC isquémico[10,44,45], hemorragias *major*[20] e mortes relacionadas com eventos vasculares[10,20]. Uma consequência lógica é que o apixabano apresenta um menor número de descontinuações por eventos vasculares, com os doentes a permanecerem mais tempo em tratamento (com os benefícios associados em termos de prevenção de eventos tromboembólicos). Por outro lado, a menor taxa de descontinuação do tratamento justifica o aumento relativo dos custos totais da terapêutica com apixabano ao longo da vida face aos outros NOAC.

Foram, no entanto, recentemente publicados outros estudos, para a realidade norueguesa[33] e para o Reino Unido[32,34], cujos resultados diferem dos presentes, no sentido em que dabigatrano foi considerado custo-efetivo *versus* apixabano (ambos superiores ao rivaroxabano). Nestes estudos, os QALY incrementais foram 0,2 a 1,3% superiores com dabigatrano *versus* apixabano, apesar do número de eventos vasculares ser determinado a partir dos mesmos ensaios clínicos considerados no presente estudo.

Vários aspetos metodológicos podem justificar estas diferenças: 1) diferenças na modelização; 2) utilização de diferentes taxas de descontinuação por outras causas; 3) modelização da mortalidade após o período do ensaio; 4) utilização de diferentes valores de utilidade associados a cada estádio (no presente estudo foram estimados com base em Sullivan et al. em 2011[30], enquanto nos outros estudos foram utilizados os valores reportados pelo mesmo autor em 2006[46]); 5) taxas de atualização diferentes.

Todas as diferenças referidas anteriormente, à exceção da primeira, foram alvo da análise de sensibilidade univariada, a qual confirmou a robustez dos resultados de base obtidos neste estudo. Logo, não é por via de qualquer um destes parâmetros que se podem explicar as diferenças nos resultados. Fica a hipótese de as diferenças entre os estudos assentarem em modelizações distintas.

As diferenças na modelização abarcam várias dimensões, incluindo a especificação de diferentes estádios nos modelos Markov, diferente duração dos ciclos e a especificação de apenas um nível de gravidade para os AVC isquémicos ou hemorrágicos. Outras diferenças nos estudos podem ter origem nos custos. As estimativas destes são influenciadas pelos recursos e especificidades dos cuidados de saúde de cada país, bem como por eventuais diferenças internacionais nos preços dos medicamentos. Averiguar quantitativamente estas questões fica para lá do âmbito do presente estudo.

Alguns estudos sugerem que o custo-efetividade dos NOAC está dependente do nível de controlo da hipocoagulação, sendo que estas intervenções tenderão a ser mais custo-efetivas num contexto de pior controlo de hipocoagulação. Em particular, foi estimado que a efetividade de dabigatrano será menor em doentes que se encontram bem controlados[47,48]. No entanto, nas análises de sensibilidade realizadas para este parâmetro, os resultados não se alteraram marcadamente.

Este estudo apresenta algumas limitações ao nível dos dados utilizados, particularmente os relativos ao número de eventos, uma vez que estes foram retirados de ensaios clínicos com tempos de seguimento curtos (2-3 anos) e podem não refletir os resultados reais de efetividade de cada anticoagulante. Além disso, na ausência de comparações *head-to-head* entre os NOAC, as efetividades foram estimadas de forma indireta, utilizando a varfarina como comparador comum, não possibilitando, deste modo, o controlo das diferenças nas características de base do doente, no desenho do ensaio clínico, no nível de adequabilidade do controlo da hipocoagulação, ou nos perfis de risco determinados pelo *score* $CHADS_2$ (apesar de se ter verificado que os resultados de efetividade do apixabano são consistentes na sub-população com valores médios mais elevados de $CHADS_2$)[49]. De acordo com a revisão da literatura realizada pelos autores, as estimativas de efetividade utilizadas no estudo são consistentes com os resultados das várias comparações indiretas publicadas, não se tendo verificado alterações nos resultados quando se consideraram outras estimativas de efetividade obtidas por métodos *bayesianos*[20].

Conclusão

Nesta análise de custo-efetividade, baseada em comparações indiretas, o apixabano revelou-se custo-efetivo *versus* a varfarina e dabigatrano, e dominante *versus* rivaroxabano, em doentes com FA não-valvular. Estes resultados foram robustos em todas as análises de sensibilidade realizadas. Esta informação é relevante para os diferentes decisores em saúde, de forma a justificar a escolha da opção terapêutica mais adequada perante o doente individual.

Responsabilidades éticas

Proteção de pessoas e animais. Os autores declaram que para esta investigação não se realizaram experiências em seres humanos e/ou animais.

Confidencialidade dos dados. Os autores declaram que não aparecem dados de pacientes neste artigo.

Direito à privacidade e consentimento escrito. Os autores declaram que não aparecem dados de pacientes neste artigo.

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Conflito de interesses

Os autores declaram não haver conflito de interesses.

Apêndice. Material adicional

Pode consultar o material adicional para este artigo na sua versão eletrónica disponível em doi:10.1016/j.repc.2015.07.004.

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ORIGINAL PAPER

Non-vitamin K antagonist oral anticoagulants in the cardioversion of patients with atrial fibrillation: systematic review and meta-analysis

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Abstract
Background Non-vitamin K antagonist oral anticoagulants (NOACs) are at least non-inferior to Vitamin K Antagonists (VKAs) for stroke prevention on patients with non-valvular atrial fibrillation (AF). We aimed to evaluate the efficacy and safety of NOACs in patients undergoing cardioversion through a systematic review and meta-analysis.
Methods MEDLINE, Cochrane Library, and Web of Science® databases (until September 2014) were searched for studies fulfilling inclusion criteria. Two reviewers independently selected randomized controlled trials (RCTs) evaluating NOACs and VKA in patients with AF undergoing cardioversion. The primary outcome was ischemic stroke or systemic embolism (IS/SE). Secondary outcomes were major bleeding, myocardial infarction, and mortality. Risk ratio (RR) and 95 % confidence intervals were derived through random-effects meta-analysis. Heterogeneity was evaluated through I^2 test.
Results Four RCTs (3 post-hoc analysis) evaluating apixaban, dabigatran, and rivaroxaban in 3,512 patients with AF were included. The risk of IS/SE with NOACs was similar to VKA (RR 0.60, 95 % CI 0.20–1.80; $I^2 = 17$ %). There was no significant increase in major bleeding (RR 1.27, 95 % CI 0.58–2.81; $I^2 = 0$ %), myocardial infarction (RR 0.71, 95 % CI 0.10–5.04; $I^2 = 0$ %), or mortality (RR 0.87, 95 % CI 0.24–3.08; $I^2 = 0$ %) with NOACs.
Conclusions This systematic review and meta-analysis suggests that NOACs may be as safe as VKAs in the setting of AF cardioversion.

Keywords Meta-analysis · Electric countershock · Stroke · Anticoagulants · Cardioversion · Transesophageal echocardiography

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Introduction

Cardioversion is used to restore sinus rhythm in patients with AF, and is done through the administration of antiarrhythmic drugs (pharmacological cardioversion) or electrical cardioversion. In patients with symptomatic AF or with hemodynamic instability, cardioversion can improve hemodynamics, functional status, and quality of life [1]. However, this procedure is associated with an increased risk of stroke, which may result from atrial thrombi dislodgement when sinus rhythm is restored [2]. To prevent these embolic events, patients with AF duration >48 h should have therapeutic anticoagulation with Vitamin K Antagonists (VKAs) for at least 3 weeks, or undergo transesophageal echocardiography to document the absence of intracardiac thrombus pre-cardioversion and fast-acting parenteral anticoagulation (with heparin) administered [3]. Patients with AF duration clearly lasting less than 48 h may be candidates to cardioversion with heparin without requiring TEE. Post-cardioversion anticoagulation is needed for a minimum of 4 weeks, or indefinitely in the presence of stroke risk factors.

Non-vitamin K oral anticoagulants (NOACs) have been evaluated in large clinical trials. In contrast to VKAs, NOACs have a lower risk of major bleeding events such as intracranial hemorrhage [4], a faster onset of action, a predictable dose–response relationship, and does not require frequent anticoagulation intensity evaluation, similar to INR testing in patients treated with VKA [5]. Different from ximelagatran (an oral anti-IIa inhibitor withdrawn due to the high risk of liver injury), recent NOACs did not show increased risk of drug-induced liver injury [6].

The NOACs have been assessed in RCTs and various systematic reviews for their efficacy and safety in patients with atrial fibrillation (AF) [7–10]. We are unaware of any prior systematic review of NOACs when used for cardioversion of AF. In the present analysis, we performed the first systematic review and meta-analysis to assess the efficacy and safety of NOACs in patients with AF undergoing cardioversion.

Methods

For the purposes of this systematic review, we followed PRISMA guidelines [11].

The protocol was published in PROSPERO website (http://www.crd.york.ac.uk/PROSPERO/) with the following registration number CRD42014013561.

Study selection and data collection

We intended to identify randomized clinical trials (RCTs) comparing NOACs (apixaban, dabigatran, edoxaban, or rivaroxaban) with Vitamin K Antagonists including or not including heparin (unfractionated or low-molecular weight), published until September 2014. We searched Medline, the Cochrane Collaboration Database and Web of Science. For search strategy details see appendix online. No language restrictions were applied.

Studies were required to include patients with AF or atrial flutter undergoing cardioversion (pharmacological or electrical) treated with NOACs or VKAs. Despite their individual pharmacokinetic and pharmacodynamic differences, NOACs share many similarities, and thus we assumed that these drugs could have a class effect. Studies had to report detailed data about the pretended outcomes in each treatment arm.

Titles and abstracts of records were screened independently by two authors. Doubts and disagreements were solved by a third person. Selected studies were assessed in full text to determine its appropriateness for inclusion. Data about patients' characteristics, antithrombotic strategies, and data of required outcomes were retrieved. In some trials, investigators were able to suspend temporarily the study medication and give open-label VKA for cardioversion. Thus, to evaluate NOACs effect in this context (without any possible interference of open-label VKA), on-treatment analysis data were retrieved whenever possible.

The Cochrane Collaboration Tool was used to assess risk bias and to evaluate reporting quality through the following items: random sequence generation method, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, description of withdrawals, and any other risk of bias features [12].

Outcome measures

The primary outcome was short-term (30–42 days) post-cardioversion ischemic stroke or systemic embolism (IS or SE). The secondary outcomes were major bleeding, myocardial infarction, and mortality, during the same time frame.

Statistical analysis

Statistical analyses were performed using RevMan 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Individual studies and meta-analysis estimates were derived, and presented in forest plot graphs.

For the meta-analysis, we used the random-effects model weighted by the inverse-variance method to estimate pooled risk ratios (RRs) and 95 % confidence intervals (95 % CIs) [13]. This method was used by default, independent of the heterogeneity of the pooled analysis. RRs were chosen to report the results because relative measures

tend to be more similar across studies compared to absolute estimates in populations having different baseline characteristics and lengths of follow-up [14]. When zero cells were present in one arm, RevMan automatically added 0.5 to them to perform the calculations.

Heterogeneity was evaluated through the I^2 test that measures the percentage of total variation between studies due to heterogeneity [15]. Heterogeneity was considered to be significant if $I^2 \geq 50$ %.

A subgroup analysis was planned according to the strategy considered for cardioversion: transesophageal echocardiogram (TEE)-guided strategy, or cardioversion without TEE.

Publication bias was assessed through visual inspection of funnel plot asymmetry. Egger's and Peters tests were performed to assess objectively this risk [16, 17].

Results

After removal of duplicates the electronic database search yielded a total of 54 studies. Following our inclusion and exclusion criteria we included four trials for analysis [18–21].

Supplementary Fig. 1 shows the detailed search strategy.

Description of studies

The four studies reported data of 3,512 patients with AF that underwent cardioversion treated with anticoagulant drugs (2200 NOACs vs. 1312 VKA) [18–21].

There was one cardioversion-based Phase 4 RCT (X-VeRT) [21], and three post-hoc analysis of Phase 3 RCTs [18–20].

Qualitatively, the overall risk of reporting bias was moderate. Supplemental Fig. 2 shows the classification according to The Cochrane Collaboration Tool.

The X-VeRT trial (rivaroxaban vs. VKA) had an open-label design as did the RE-LY study (dabigatran vs. VKA) [18, 21]. The remaining studies had double-dummy double-blinded designs [19, 20]. Because none of the studies were properly powered; we classified all studies as having high risk of bias in 'other bias' field.

Data were heterogeneous regarding the use of transesophageal echocardiography before cardioversion. The use of this technique to exclude intracavitary thrombus ranged from 21 to 64 %. TEE was most commonly used in early elective cardioversions (X-VeRT) [21].

Table 1 details the main characteristics of the various studies.

Ischemic stroke and systemic embolism

Primary outcome data were available from four studies. Overall 3,512 patients undergoing cardioversion were evaluated. One trial reported zero events in both arms and was excluded for the primary analysis [18]. The risk of IS or SE with NOACs was not different from the standard approach using VKA: RR 0.60, 95 % CI 0.20–1.80; $I^2 = 17$ % (Fig. 1).

Secondary outcomes

The incidence of major bleeding with NOACs was reported in three studies (3,208 patients), and NOACs were not statistically different from VKA, with a RR 1.27 and 95 % CI 0.58–2.81 (Fig. 2a). Myocardial infarction (RR 0.71, 95 % CI 0.10–5.04; Fig. 2b) and mortality (RR 0.87, 95 % CI 0.24–3.08; Fig. 2c) incidences were not different among interventions. No heterogeneity was noticed in any evaluation of secondary outcomes ($I^2 = 0$ %).

Subgroup analysis according to the use of transesophageal echocardiogram

Three RCTs provided data for the primary outcome in the subgroup of patients undergoing a transesophageal echocardiogram-guided cardioversion. For RE-LY trial we considered in the denominator the number of cardioversions because we were unable to retrieve the number of patients treated in each arm with this strategy (some patients had more than one cardioversion). Meta-analysis showed that patients treated with NOACs undergoing TEE-guided cardioversion had a non-significant RR 0.18 (95 % CI 0.02–1.35; $I^2 = 0$ %). This estimate was not different (p value for interaction = 0.28) from pooled analysis of NOACs vs. VKA in patients that did not perform TEE before cardioversion (RR 0.75, 95 % CI 0.15–3.76; $I^2 = 19$ %). Figure 3 shows the forest plot of subgroup analyses.

Analyses using Peto's odds ratio and risk difference measures

We further explored the impact of using different effect measurements on pooled estimates, because the events' rates were low or null in some studies [22–24].

Peto's odds ratio (OR) in circumstances of rare events has been reported to be an adequate and more reliable effect measurement for dichotomous outcomes [22]. Risk difference (RD) is a measure that has the advantage to consider studies with zero events in both arms for meta-analysis estimate [22, 23].

Table 1 Main characteristics of RCTs included in the review

Study	Type of study	Population	Mean age/ female (%)	Number CV/ TEE (%)	Electrical/ pharmacological CV	Urgent or emergent cardioversions	Post-cardioversion outcomes	Primary outcome
ARISTOTLE	Post-hoc analysis of a double-blinded RCT	540 patients (OTA 451 patients) 228 Apixaban vs. 223 VKA	67; 27 %	609/33.3 %	N/R	N/R In the ITT analysis there were 4 lethal events. The CV was urgent/emergent in 3 of these patients	30-day SSE; MI, MB and Mortality	SSE
RE-LY	Post-hoc analysis of a open-label RCT	1,270 patients 834 Dabigatran Etexilate vs. 436 VKA	N/R	1,983/ 21.0 %	83.7/16.3 %	N/R CV was urgent/emergent in 3 of the 7 deaths registered	30-day SSE and MB	SSE
ROCKET-AF	Post-hoc analysis of a double-blinded RCT	285 patients (OTA 245 patients) 124 Rivaroxaban vs. 121 VKA	N/R	375/N/R	48.3 %/51.7 %	N/R	30-day SSE	SSE
X-VeRT	Open-label RCT designed to assess outcomes after elective CV	1,504 patients 978 Rivaroxaban vs. 492 VKA	65/27 %	Early CV 872/64.7 % Delayed CV 632/10.1 %	>90 % electrical CV	None	42-day SSE; MI, MB, and mortality	42-day SSE, MI, and cardiovascular death

CV cardioversion INR, *ITT* intention-to-treat, *MB* major bleeding, *MI* myocardial infarction, *N/R* not reported, *OTA* on-treatment analysis, *RCT* randomized controlled trial, *SSE* stroke or systemic embolism, *TEE* transesophageal echocardiogram

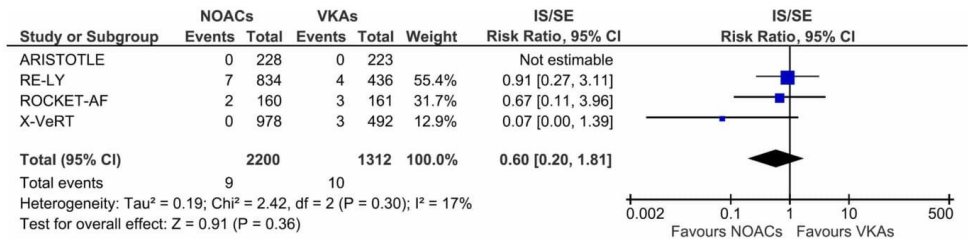

Fig. 1 Forest plot of NOACs vs. VKAs for ischemic stroke or systemic embolism (primary outcome)

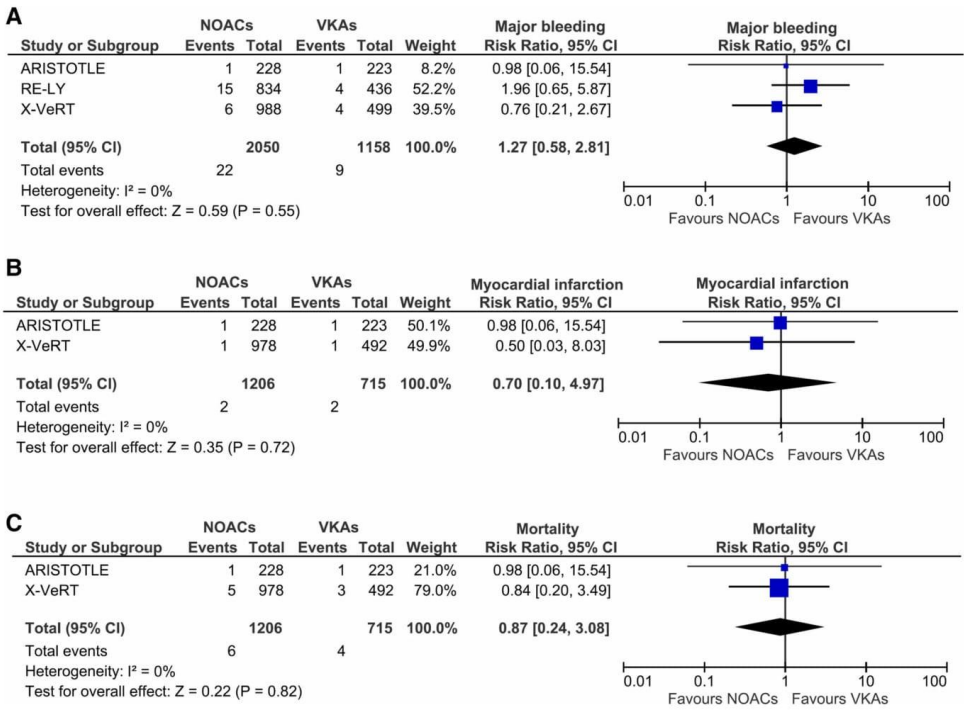

Fig. 2 Forest plots of NOACs vs. VKAs for: **a** major bleeding; **b** myocardial infarction; **c** mortality

For the primary outcome, IS or SE, NOACs and VKA were not statistically different using Peto's OR as a summary measure: Peto's OR 0.54 (95 % CI 0.21–1.37) with a significant heterogeneity ($I^2 = 56$ %). Using RD for the primary outcome allowed us to include ARISTOTLE data in the quantitative evaluation. Pooled analysis of 4 trials with 3,512 patients showed a non-significant RD decrease of −0.3 % (95 % CI −0.8 to 0.2 %) without heterogeneity ($I^2 = 0$ %) (Fig. 4). The results for secondary outcomes are exposed in Table 2.

Publication bias

The small number of included studies does not allow an adequate visual evaluation of publication bias risk (supplementary Fig. 3) [25]. Egger's ($p = 0.27$) and Peters

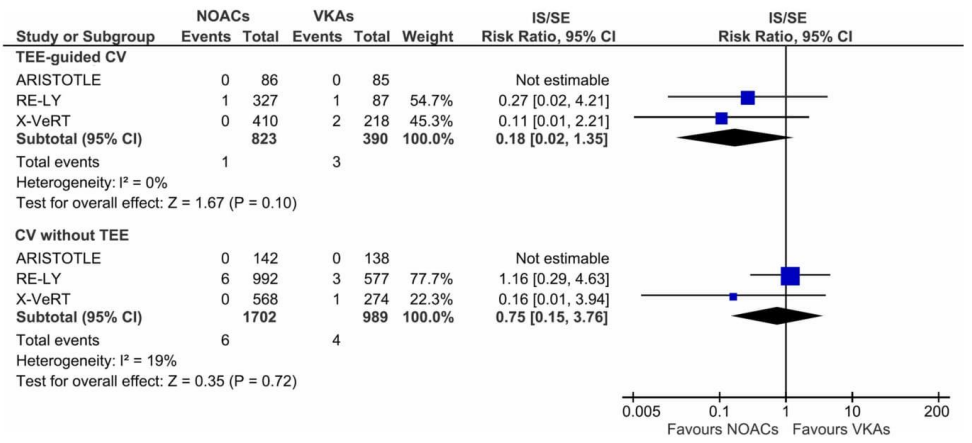

Fig. 3 Forest plot of NOACs vs. VKAs for ischemic stroke or systemic embolism (IS/SE) according to the use of transesophageal echocardiogram (TEE) before the cardioversion (CV)

Table 2 Results of pooled analysis according to summary measures

	RR (95 % CI); I^2 (%)	RCTs; patients	Peto's OR (95 % CI); I^2 (%)	RCTs; patients	RD (95 % CI); I^2 (%)	RCTs; patients
IS or SE	0.60 (0.20, 1.81); 17 %	3; 3,061	0.54 (0.21, 1.37); 56 %	3; 3,061	−0.3 % (−0.8, 0.2); 0 %	4; 3,512
Major bleeding	1.27 (0.58, 2.81); 0 %	3; 3,208	1.31 (0.62, 2.75); 0 %	3; 3,208	0.1 % (−0.5, 0.8); 0 %	3; 3,208
Myocardial infarction	0.71 (0.10, 5.04); 0 %	2; 1,921	0.70 (0.09, 5.24); 0 %	2; 1,921	−0.09 % (−0.5, 0.3); 0 %	2; 1,921
Mortality	0.87 (0.24, 3.08); 0 %	2; 1,921	0.86 (0.24, 3.17); 0 %	2; 1,921	−0.01 % (−0.8, 0.6); 0 %	2; 1,921

IS ischemic stroke, *OR* odds ratio, *RCTs* randomized controlled trials, *RD* risk difference, *RR* risk ratio, *SE* systemic embolism

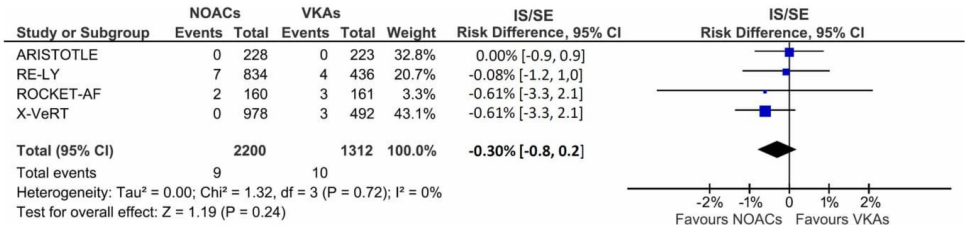

Fig. 4 Forest plot of NOACs vs VKAs for ischemic stroke or systemic embolism, using risk difference measure

($p = 0.91$) tests were not suggestive of publication bias risk

Discussion

Taken together, this systematic review and meta-analysis summarizes the best available evidence on NOACs for cardioversion of AF. The principal findings of our study are the following: (1) NOACs were as safe as VKA in the prevention of stroke or systemic embolism in patients undergoing cardioversion; (2) The rate of primary events was very low in the four studies and in both therapeutic arms (19 events in 3,500 patients). The confidence intervals of estimates were still wide and pooled data were not powered enough to establish non-inferiority of NOACs

compared to VKA [21], nonetheless, the data provided information about the safety of NOACs in this context. (3) The rates of other clinically significant outcomes such as major bleeding, myocardial infarction, and mortality did not differ significantly among interventions.

Anticoagulation is known to reduce the risk of stroke or systemic embolism in the cardioversion setting [2, 26]. It is recommended that effective anticoagulation for a minimum of 3 weeks before cardioversion when AF duration is >48 h (delayed cardioversion method) is needed, while post-cardioversion anticoagulation is required for at least 4 weeks to prevent embolic events related to atrial stunning/incomplete atrial contraction recovery or early AF recurrences [27, 28].

Transesophageal echocardiogram allows physicians to accurately diagnose or exclude thrombus in the left atrial appendage or in other cardiac chambers. The exclusion of intracavitary thrombi enables immediate cardioversion using a fast-acting anticoagulant (immediate cardioversion method), with post-cardioversion events similar to the delayed method [3]. In this review we performed a meta-analysis of subgroups of patients undergoing a transesophageal echocardiogram-guided strategy and the results showed a trend favoring NOACs regarding IS or SE, thus ensuring the safety of these drugs using this strategy. In stable AF patients with a TEE without intracardiac thrombus, cardioversion should only be performed under adequate antithrombotic environment. If no drugs were given before, physicians should be aware that NOACs only have their effective onset of action about 4 h after oral intake [21].

In our review we evaluated whether TEE guidance improves the safety of cardioversion under NOACs; there was a trend toward higher safety with undergoing TEE which could be due to underpowered comparisons despite the meta-analysis.

Due to the linear relationship of dose–effect, NOACs provide effective anticoagulation as long as the medication adherence is warranted. This is particularly important in the delayed cardioversion because the classical anticoagulation with VKA is susceptible to INR fluctuations, leading to sub-therapeutic levels and increased thrombotic burden [29]. Furthermore sub-therapeutic INR levels are an important source of costs related to postponement of the cardioversion procedure [30]. In patients undergoing immediate cardioversion, NOACs have a fast onset of action, without the need of further bridging or switching anticoagulants after performing the cardioversion [31].

Altogether the results of this review are of interest to all stakeholders:

Patients now have a safe and convenient alternative to VKA, without the need of serial analysis of hemostatic parameters, and cardioversions are postponed due to ineffective anticoagulation.

Indeed, physicians can reliably consider patients for effective anticoagulation with NOACs before, during, and after cardioversions, without the need for switching or bridging. Nevertheless it is of capital importance to assess the medication adherence in the 3 weeks before a cardioversion, and in case of doubt about compliance a TEE-guided strategy should be considered [32, 33]. Once-daily dosing regimens are classically associated with improved medication adherence [34], but in this context, particularly with NOACs, data are scarce. Nevertheless, only twice-daily regimens (apixaban and dabigatran 150 mg) have shown to decrease significantly the risk of stroke compared to VKA [35].

For policymakers, NOACs can also decrease costs associated with elective cardioversion cancelations or postponements, as occurs frequently with patients treated with VKA.

"Real-world" observational data are scarce but are consistent with our findings, highlighting the safety of NOACs in cardioversion [36]. The ongoing phase 4 RCTs ENSURE-AF trial using edoxaban (aiming for a sample size of 2,200 patients) [37], and EMANATE trial using apixaban (planned to enroll 1,500 patients) [38], will provide more robust data of cardioversions with NOACs. These trials will be also underpowered and, albeit unknown, it is not probable that a meta-analysis after data dissemination will be able to answer any of the relevant questions. According to sample size calculation of X-VeRT, a sample size of 25,000–30,000 patients would be required to properly answer clinically relevant questions in this context.

Limitations

This analysis is limited by methodological issues associated with meta-analysis and individual studies. The results of our meta-analysis are based on study-level data and not on individual patients' data.

The overall quality of included studies moderate: we considered that most of the trials were at high risk of selective reporting bias due to the unplanned nature of the analysis of patients undergoing cardioversion; two of the trials were performed with an open-label design; and none of the studies were properly powered to answer the question raised.

Data for some outcomes were not available and restrains our review for robust conclusions.

Pooling data of studies with different designs (confounding bias in observational studies) that evaluated patients in different settings (elective cardioversions and acute hospitalization cardioversions; referral bias) should also be accounted as limitations to our conclusions.

Nevertheless, it increases the power and external validity of the data obtained.

We also pooled the different NOACs under the assumption of a class effect of these drugs in cardioversion. Despite the pharmacodynamic and pharmacokinetic differences among NOACs [32, 34], there were no significant differences of estimates in the meta-analysis.

Conclusions

The best available evidence is underpowered to establish non-inferiority of NOACs compared to VKA. However, our meta-analysis suggests that NOACs (apixaban, dabigatran, and rivaroxaban) may be as safe as VKA for stroke and systemic embolism prevention in AF patients undergoing cardioversion. Other outcomes of interest such as major bleeding, myocardial infarction, and mortality were not different between NOACs and VKA.

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Conflict of interest DC, and JC do not have any competing interests to disclose. JJF had speaker and consultant fees with GlaxoSmithKline, Novartis, TEVA, Lundbeck, Solvay, Abbott, Bial, Merck-Serono, Grunenthal, and Merck Sharp and Dohme. GYHL had consultant fees from Bayer, Astellas, Merck, Astra Zeneca, Sanofi, BMS/Pfizer, Biotronik, Portola, and Boehringer Ingelheim; and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi-Aventis. FJP had consultant and speaker fees with Astra Zeneca, Bayer, and Boehringer Ingelheim.

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Letter to the Editor

Thromboembolic risk in the initiation, switch and interruption/re-initiation of oral anticoagulants: Do newcomers improve outcomes? Insights from a meta-analysis of RCTs

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Anticoagulation is the cornerstone treatment in patients with atrial fibrillation for stroke prevention. In the last decades, oral vitamin K antagonists (VKA) have been the most used drug of this class. The clinical management of these patients is not straightforward due to the need of periodical evaluation of the INR, as well as due to the numerous drug–drug and drug–food interactions. In addition, recent studies have provided new insights of potential problems associated with VKA treatment:

a) The initiation of VKA itself does not seem to be an uneventful procedure. According to the results of a retrospective case–control study, Azoulay and colleagues point to the existence of a 30 day period with increased risk of thromboembolic events after the initiation of VKA [1].
b) This study points to the possibility of a liability period, as suggested by the results of ROCKET-AF post trial follow-up, where patients crossing from rivaroxaban to anticoagulants (only 3% took aspirin) had increased risk of thromboembolic events [2].
c) It is also known that temporary discontinuation of anticoagulation leads to impaired hemostasis in patients undergoing invasive interventions, which carries some risk. Furthermore, some of these receive periprocedural bridging treatment (e.g. low-molecular weight heparin) which is associated with an increased risk of bleeding [3].

All these aspects highlight the need for increasing the knowledge about interventions that decrease the risk associated with the referred situations.

Recently, IIa and Xa direct inhibitor oral anticoagulants have reached the market overcoming some of the limitations associated with VKA. These non-vitamin K antagonist oral anticoagulants (NOACs) have a predictable dose–response profile, a faster onset of action compared to VKA, and do not require any kind of control of hemostasis parameters.

Therefore it would be of interest to further evaluate quantitatively the overall risk of 30-day risk of thromboembolic events in patients with atrial fibrillation through random-effects meta-analysis data from phase III randomized controlled trials (data retrieved from NOACs published trials [4–7], substudies [2,8–10], and unpublished public reports from regulatory entities). In particular, we aimed to assess: a) risk of thromboembolic events during the initiation of VKA; b) risk of thromboembolic events during the switching period to VKA; c) whether NOACs mitigate the anticoagulant initiation risk of thromboembolic events; and d) whether NOACs decrease the thromboembolic risk associated with temporary drug discontinuation. We expected that this methodology would determine, with improved power and precision, the direction, size (Risk Ratio [RR] and 95% Confidence Interval [95% CI]) and consistency (I^2 test) of effects across studies.

Compared to VKA-experienced patients, the initiation of this drug in VKA-naïve patients was associated with a significant increased risk of thromboembolic events (RR 1.79; 95% CI: 1.05 to 3.06; $I^2 = 0\%$; 3 trials; 22,185 patients), similar to that reported by Azoulay and colleagues (RR 1.71; 95% CI: 1.39 to 2.12).

Open-label switch from NOACs to VKA at the end of trials was associated with a 4-fold increase of thromboembolic risk comparing to patients maintaining VKA (RR 4.18; 95% CI: 2.16 to 8.08; $I^2 = 0\%$; 3 trials; 21,799 patients).

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With respect to whether NOACs can mitigate this oral anticoagulant effect, our analysis showed that NOAC thromboembolic rates were not different from VKA-experienced patients (RR 0.81; 95% CI: 0.34 to 1.90; $I^2 = 35\%$) but had a trend favouring NOACs when compared to VKA-naïve cohorts (RR 0.47; 95% CI: 0.20 to 1.11; $I^2 = 48\%$; 3 trials; 22,228 patients).

The risk of thromboembolic events associated with the temporary drug discontinuation was similar between NOACs and VKA (RR 1.01; 95% CI: 0.68 to 1.49; $I^2 = 0\%$; 3 studies; 15,737 patients).

Fig. 1 shows the main results of the meta-analysis. This analysis is limited by the risk of bias associated with the lack of adjustment of results to baseline characteristics differences. Pooling the results at study-level also increases the risk of bias particularly when different populations are included in the analysis. Incompleteness of detaileddata also impairs the strength of conclusion (e.g. 3% of rivaroxaban patients were switched to antiplatelet treatment). Recognizing the problem inherent to anticoagulant switch, an end-of-trial transition plan (with frequent INR evaluations and a VKA titration algorithm) was proposed for ENGAGE AF-TIMI 48 trial (edoxaban vs. VKA) whose results will provide further knowledge on this topic.

In conclusion, our results suggest that:

1) The initiation of VKA (ad initio or switching from NOACs) is consistently associated with a clinical relevant and statistical significant increased risk of thromboembolic events, reinforcing the data from Azoulay and colleagues;
2) NOACs may decrease this risk in such circumstances; and
3) When temporary drug interruption (and subsequent reinitiation) is required, NOACs and VKA have similar thromboembolic risk.

Conflict of interest

DC and JC do not have any competing interests to disclose. JJF had speaker and consultant fees with GlaxoSmithKline, Novartis, TEVA,

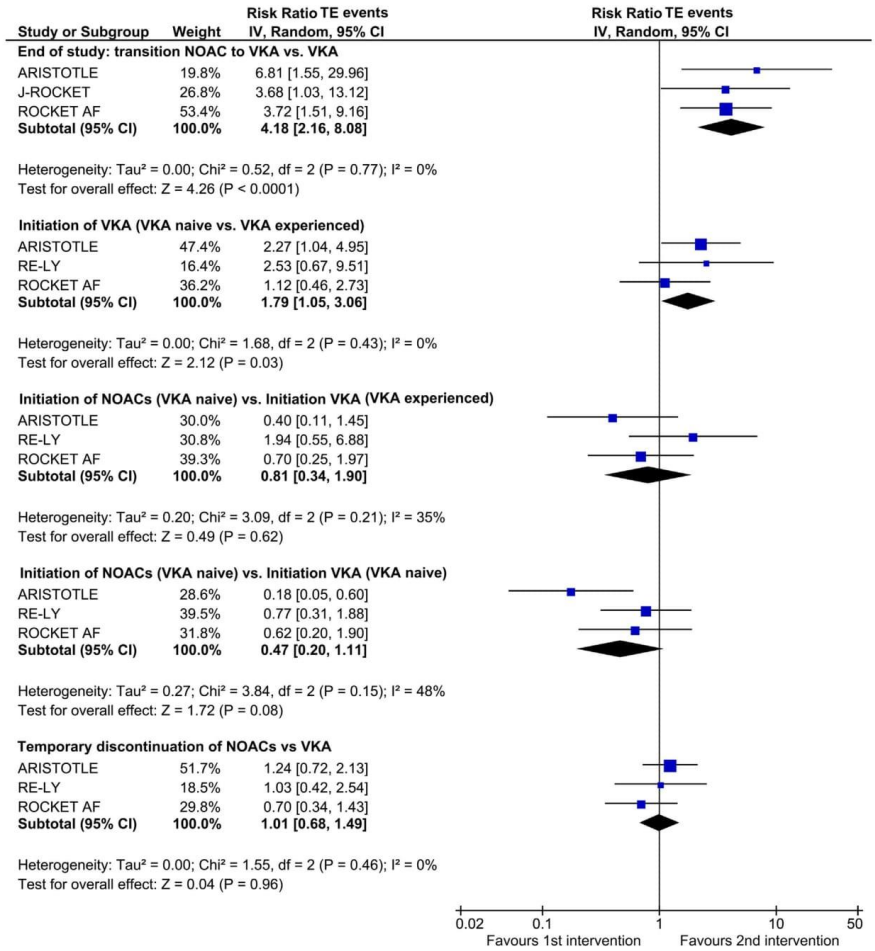

Fig. 1. Forest plot with results of the meta-analysis. NOACs: Non-vitamin K antagonist oral anticoagulants; TE: Thromboembolic; VKA: Vitamin K antagonists.

Lundbeck, Solvay, Abbott, Bial, Merck-Serono, Grunenthal, and Merck Sharp and Dohme. FJP had consultant and speaker fees with Astra Zeneca, Bayer and Boehringer Ingelheim. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

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THE AUTHORS REPLY: Santos-Gallego and Badimon hypothesize that patients who underwent PCI reperfusion within the first 120 minutes after the onset of ischemia might benefit from the protection afforded by cyclosporine. To our knowledge, there is no experimental evidence that cyclosporine might be more effective after a short period of ischemia. In our study, cyclosporine did not salvage myocardial tissue, regardless of the duration of ischemia, including in the 12.5% of patients with less than 2 hours of ischemia. The 87.5% of patients with 2 hours of ischemia or more, in whom larger infarcts developed and who had a worse clinical outcome, would certainly have had the most benefit from any protection against reperfusion injury.

Pottecher et al. suggest that confounders, including preexisting angina, coronary collateral vessels, or diabetes may explain the lack of a protective effect of cyclosporine. Previous phase 2 trials have shown that postconditioning angioplasty reduces infarct size, although some patients might have had preexisting angina.[1,2] A per-protocol analysis showed that exclusion of patients with coronary collateral vessels did not modify the CIRCUS results. Experimental data suggest that hyperglycemic (but not diabetic) animals may be resistant to postconditioning induced by brief episodes of ischemia and reperfusion but not by cyclosporine. Transient hyperglycemia in patients with acute myocardial infarction may be indicative of a sympathetic system activation but not of diabetes. To our knowledge, there is no evidence so far that diabetes might prevent any cyclosporine-induced protection.

Zografos and Katritsis hypothesize that clopidogrel might have interfered with the pharmacokinetic properties of cyclosporine and prevented its protective effect. Only 2.7% of the patients in our trial received clopidogrel, whereas 63.2% received prasugrel and 34.1% received ticagrelor. We have no evidence that clopidogrel had any effect on cardiovascular events.

Bernardi and Di Lisa propose that after its binding to cyclophilin D, cyclosporine delays, but does not fully inhibit, the PTP, which might explain the lack of effect in patients with acute myocardial infarction. However, pharmacologic or genetic inhibition of cyclophilin D is sufficient in most animal models to significantly reduce infarct size.[3] Prolonged administration of cyclosporine may certainly be detrimental after acute myocardial infarction, mainly because it might facilitate adverse left ventricular remodeling.[4] However, a single intravenous injection of cyclosporine was used in this trial, and we did not observe any related increase in left ventricular remodeling. We agree that the results of CIRCUS do not challenge the concept of reperfusion injury.

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Since publication of their article, the authors report no further potential conflict of interest.

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Bridging Anticoagulation in Patients with Atrial Fibrillation

TO THE EDITOR: Douketis et al. (Aug. 27 issue)[1] report on the results of the Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) trial. They conclude that in patients with atrial fibrillation who required an operation or procedure, a strategy of discontinuing warfarin treatment without

the use of bridging anticoagulation was noninferior to the use of bridging anticoagulation for the prevention of arterial thromboembolism.

However, in the study methods, they did not take into account silent stroke. Silent stroke is defined as the evidence of infarction on brain imaging without a clinical finding of acute neurologic deficit related to that lesion. The prevalence of silent stroke is much higher than the prevalence of stroke with neurologic deficit,[2] especially among patients with atrial fibrillation[3] and those who are undergoing high-risk procedures,[4] and it is associated with long-term complications (e.g., neurocognitive dysfunction and psychiatric disorders).[5]

We think this is an important study that will improve care for selected patients who receive anticoagulation therapy yet need procedures that require temporary discontinuation of this therapy. However, we think there is a need for caution until future studies include an assessment of silent stroke and its effect on function.

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Dr. Jagoda reports being a member of Brain Attack Coalition and serving on advisory boards for Pfizer, Boehringer Ingelheim, and AstraZeneca. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The central question about the BRIDGE trial is whether it investigated the right target population of patients who were undergoing the relevant target procedures. First, most of the patients were classified as having a low risk of thromboembolism. The mean $CHADS_2$ score ($CHADS_2$ scores range from 1 to 6, with higher scores indicating a greater risk of stroke) of the patients was 2.3, and patients with high $CHADS_2$ scores (5 or 6) composed only 3% of the study population. Among these latter patients, annual stroke rates range from 12 to 18%.[1] This high risk of stroke probably exceeds the risk of major bleeding; therefore, this group of patients might benefit from bridging therapy.

Second, the majority of the patients underwent procedures such as gastrointestinal endoscopy (including biopsies) that are associated with a low risk of bleeding. There is general consensus that these procedures can be performed while the patient is continuing to receive anticoagulation therapy.[2] Data are lacking from a trial that compares forgoing bridging with bridging with low-molecular-weight heparin in patients who have a moderate-to-high risk of arterial thromboembolism and a $CHADS_2$ score of 5 or 6 and who are undergoing major surgery such as carotid endarterectomy and major surgery for cancer.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In the BRIDGE trial, bridging with low-molecular-weight heparin significantly increased the risk of major bleeding without decreasing the risk of thromboembolism among patients with atrial fibrillation who were deemed to require interruption of vitamin K antagonists for invasive procedures. It was surprising that the rate of myocardial infarction was not significantly higher in the bridging group than in the no-bridging group (1.6% vs. 0.8%), although fatal

myocardial infarctions were observed only in the no-bridging group (two of seven patients with myocardial infarction died). It would be useful to know whether these events were due to ischemic imbalance related to major bleeding (myocardial infarction type 2)[1] rather than to thrombotic events.

Temporary discontinuation of vitamin K antagonists and non–vitamin K antagonist oral anticoagulants leads to a similar thromboembolic risk[2,3] and, as with vitamin K antagonists, a higher bleeding risk occurs with bridging during discontinuation of non–vitamin K antagonist oral anticoagulant therapy.[2] Because of the pharmacologic properties of non–vitamin K antagonist oral anticoagulants, caution is needed in applying the results of the BRIDGE trial to patients with atrial fibrillation who receive these agents. The usefulness of low-molecular-weight heparin may be limited to patients with immobility who require early postoperative venous thromboprophylactic anticoagulation, with deferred resumption of full-dose anticoagulation.[4] To our knowledge, the use of non–vitamin K antagonist oral anticoagulants at a reduced or thromboprophylactic dose in patients with atrial fibrillation has not yet been studied.[4]

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No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1513255

TO THE EDITOR: We think that the study reported by Douketis et al. is highly relevant, since every year, nearly 250,000 North Americans require interruption of an oral anticoagulant for invasive procedures.[1] The question of "to bridge or not to bridge" poses a conundrum for many providers.

There are two issues that we think, if expanded on, would allow better applicability of the findings of the trial. First, the authors do not provide specific reasons why 544 patients were withdrawn from enrollment by their physicians. Since clinicians need to use their judgment in weighing the risks and benefits of anticoagulant bridging, further information about patients who were deemed to be too high risk for study inclusion would be useful.

Second, it would be helpful to evaluate the association between bleeding prediction formulas (e.g., the Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly [>65 years], Drugs/Alcohol Concomitantly [HAS-BLED] score) and the risk of periprocedural bleeding in both trial groups, since this information may help determine whether these scores predict which patients may benefit from a specific strategy. Although this study is timely, we think that the additional information we suggest would help providers use a more targeted, patient-specific approach in clinical practice.

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DOI: 10.1056/NEJMc1513255

TO THE EDITOR: I would like to call attention to one issue of concern in the article by Douketis et al. As stated in the Discussion section, choosing a noninferiority margin of 1.0%, not depending on the actual rate of thromboembolic events (absolute risk), increases the relative risk that is considered acceptable if the actual event rate is lower than expected.

If, as planned in the protocol, the rate of thromboembolic events had been 1.0% in the

bridging group, the relative risk that would be considered acceptable for noninferiority would have been 2.0 (calculated as the sum of 1.0% plus 1.0% divided by 1.0%). Doubling the risk would have been considered an acceptable increase in the risk of thromboembolic events in the no-bridging group.

However, since the actual risk in the bridging group is only 0.3%, the relative risk considered to be acceptable is 4.3 (the sum of 1.0% plus 0.3% divided by 0.3%). The acceptable risk with respect to the rate of thromboembolic events is thus increased by a factor of 4. I am not sure this risk should be considered to be acceptable. In practice, I think that patients for whom a no-bridging strategy will be proposed should be told that the risk of thromboembolic events will probably not be increased by more than a factor of 4.

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THE AUTHORS REPLY: Duca and Jagoda infer that detection of silent stroke would have been an important outcome to measure. This would have necessitated routine imaging to detect subclinical events, adding cost and complexity to the intentionally simple study design. Moreover, data are lacking on the incidence and clinical significance of perioperative silent stroke among patients who are undergoing types of surgery that are associated with an increased risk of stroke.[1]

Vink and colleagues question whether the findings of the BRIDGE trial are applicable to patients who have atrial fibrillation and a $CHADS_2$ score of 5 or 6 and those undergoing high-risk operations. Patients with a $CHADS_2$ score of 5 or 6 constituted 3% of the study population, but such patients are infrequently observed in clinical practice. The types of operations or procedures observed in our trial reflected those described in other studies involving patients who were assessed for bridging.[2] Overall, we interpret the results as being applicable to most patients with atrial fibrillation who are assessed for periprocedural management of anticoagulant therapy.

With regard to the comments of Caldeira et al.: because of the small number of events, we did not assess determinants that might explain the higher number of myocardial infarctions in the bridging group than in the no-bridging group. We agree that caution is needed when extrapolating the findings of our trial to patients who require interruption of a direct oral anticoagulant for an operation or a procedure.

Arbit and colleagues raise concern that 544 screened patients were deemed ineligible by their physicians. However, this number constituted only 12% of patients who were excluded for reasons other than that they might have been deemed to be too high risk to participate in the trial. A study is under way to assess predictors of perioperative bleeding in our trial and the usefulness of bleeding prediction scores, including HAS-BLED.[3]

In reply to Clapin: the use of a relative-risk measure for rare events is potentially problematic.[4] The BRIDGE trial was designed so that there was not a large difference between the rates of thromboembolic events in the no-bridging group and the bridging group. A consensus determination by clinicians was that an absolute difference of 1.0% should be ruled out to ensure that result. This was part of the original trial protocol, but it was not incorporated into the informed-consent documents. The BRIDGE steering committee was aware of the implications of the noninferiority margin on the observed lower-than-expected rate of thromboembolism but determined that it was acceptable, given the low absolute event rate and the need to adhere to the prespecified analysis plan.

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Since publication of their article, the authors report no further potential conflict of interest.

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META-ANALYSIS

Antithrombotic treatment in chronic heart failure and sinus rhythm: Systematic review

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Author contributions: Caldeira D and Costa J contributed to the concept and design of the study and acquisition, analysis and interpretation of the data, wrote the first draft of the manuscript, critically revised the manuscript, and gave final approval of the submitted manuscript; Ferreira JJ and Pinto FJ contributed to the concept and design of the study and interpretation of the data, critically revised the manuscript, and gave final approval of the submitted manuscript; Cruz I, Calé R, Martins C and Pereira H contributed to interpretation of data, critically revised the manuscript, and gave final approval of the submitted manuscript.

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Abstract

AIM: To assess the efficacy and safety of antithrombotic drugs (antiplatelet or anticoagulant drugs) compared to no antithrombotic treatment or placebo in patients with heart failure (HF) and sinus rhythm.

METHODS: We searched Medline and Cochrane Library for randomized controlled trials evaluating antithrombotic treatment and no antithrombotic treatment in patients with HF and sinus rhythm. Risk ratio (RR) and 95%CIs were estimated performing meta-analysis with random effects method.

RESULTS: Two studies met the inclusion criteria: Heart failure Long-term Antithrombotic Study and Warfarin/Aspirin Study in Heart failure, with 336 patients and mean follow-up 1.8-2.25 years. Stroke risk was not reduced by acetylsalicylic acid (RR = 1.18, 95%CI: 0.17-8.15), oral anticoagulation (RR = 0.30, 95%CI: 0.03-2.65) or overall antithrombotic drugs (RR = 0.52, 95%CI: 0.10-2.74). Acetylsalicylic acid showed a significant increased risk of worsening HF (RR = 1.78, 95%CI: 1.08-2.92), while oral anticoagulation had no impact in this outcome (RR = 1.03, 95%CI: 0.61-1.75). Overall antithrombotic drugs showed a significant risk increase of major bleeding (RR = 6.99, 95%CI: 0.89-54.64).

CONCLUSION: Best available evidence does not support the routine use of antithrombotic drugs in patients with HF and sinus rhythm. These drugs, particularly oral anti-

coagulation has the hazard of increase significantly major bleeding risk.

Key words: Heart failure; Sinus rhythm; Platelet aggregation inhibitors; Anticoagulants

Core tip: In patients with atrial fibrillation, chronic heart failure (CHF) increases thromboembolic risk and oral anticoagulation is essential to decrease the risk of thromboembolic complications. Evidence suggests a positive association between CHF, impaired hemostasis and thromboembolic events. Whether antithrombotic drugs should be recommended for these patients (in sinus rhythm) is still debated. We looked for the best available evidence and we found 2 studies fulfilling the inclusion criteria. We performed a meta-analysis of antithrombotic drugs *vs* placebo and strengthened that antithrombotic drugs do not decrease the risk of stroke (fatal or non-fatal) and increase the risk of major bleeding.

Caldeira D, Cruz I, Calé R, Martins C, Pereira H, Ferreira JJ, Pinto FJ, Costa J. Antithrombotic treatment in chronic heart failure and sinus rhythm: Systematic review. *World J Meta-Anal* 2015; 3(1): 36-42 Available from: URL: http://www.wjgnet.com/2308-3840/full/v3/i1/36.htm DOI: http://dx.doi.org/10.13105/wjma.v3.i1.36

INTRODUCTION

Chronic heart failure (CHF) is an increasingly prevalent cardiovascular disease with significant associated morbidity and mortality[1]. CHF constitutes a significant economic burden[2,3], which is expected to increase over the next decades due to increasing prevalence of associated diseases and risk factors as well as population aging. Former observational studies suggest a positive association between CHF, impaired hemostasis and thromboembolic events[4,5]. In patients with atrial fibrillation (AF), CHF increases thromboembolic risk and oral anticoagulation is the cornerstone of AF treatment aiming to decrease the risk of thromboembolic complications[6]. The results from the WARCEF trial (Warfarin *vs* Aspirin in Reduced Cardiac Ejection Fraction) has highlighted the role of antithrombotic treatment in patients with CHF and sinus rhythm[7]. There were no differences between warfarin and acetylsalicylic acid in the primary outcome (time to the first event in a composite end point of ischemic stroke, intracerebral hemorrhage, or death from any cause). However, warfarin was associated with fewer stroke events (2.5% *vs* 4.7%) but also with a higher rate of major bleeding events (5.8% *vs* 2.7%). The clinical interpretation of these findings was that the choice between warfarin and aspirin should be made on the basis of the individual patient[8].

Previous systematic reviews with meta-analyses comparing oral anticoagulation (namely warfarin) and acetylsalicylic acid in patients with CHF and sinus rhythm reached conclusions overlapping those from the WARCEF study[9-13].

Although much effort have been done comparing and discussing the relative effectiveness of oral anticoagulation *vs* acetylsalicylic acid in patients with CHF and sinus rhythm, significantly less is known about the true efficacy of the overall antithrombotic treatment. Therefore, we aimed to perform a systematic review to better estimate the true clinical benefit of antithrombotic treatments (oral anticoagulation or antiplatelet drugs) against placebo, standard care or no treatment, in patients with CHF and sinus rhythm.

MATERIALS AND METHODS

Guidance

This work followed PRISMA guidelines for systematic reviews and meta-analyses promoted by the EQUATOR network[14].

Eligibility criteria

We have searched for all randomized controlled trials (RCTs) evaluating patients with CHF and sinus rhythm treated with oral antithrombotic therapy or control. We considered for antithrombotic treatments both oral anticoagulants (such as vitamin K antagonists, like warfarin, acenocoumarol or phenprocoumon) and antiplatelet drugs [such as acetylsalicylic acid (ASA), clopidogrel or ticlopidine]. We allowed controls under placebo, standard care or no antithrombotic treatment. Studies had to report clinical and/or echocardiographic features for the enrolled CHF patients, such as impaired left ventricle ejection fraction or shortening fraction.

Database and search method

Medline and Cochrane Library (CENTRAL) databases were searched from inception to November 2013 for eligible studies. The search strategy details are available at the Online Supplementary Material. We considered all studies irrespective of language. References of obtained studies were also comprehensively searched and cross-checked to identify possible missing studies.

Studies and data selection

Citations obtained from electronic search were independently screened by two authors, followed by full-text assessment of potentially eligible studies for inclusion in accordance with previously mentioned criteria.

Primary outcome was stroke (fatal or non-fatal). Secondary outcomes were all-cause mortality, myocardial infarction, worsening heart failure (HF), major bleeding and a composite of major adverse clinical events, defined as the combination of mortality, stroke, myocardial infarction and HF.

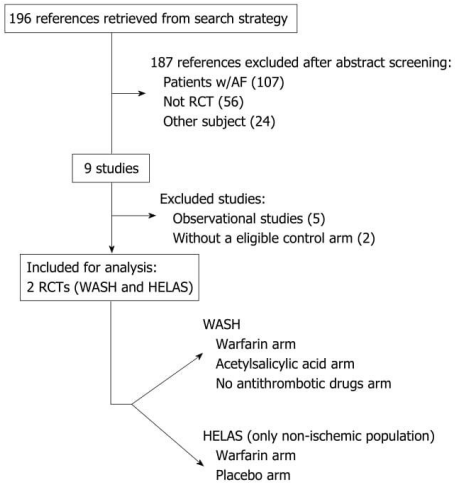

Figure 1 Flowchart of studies' selection. AF: Atrial fibrillation; RCT: Randomized controlled trial; WASH: Warfarin/Aspirin Study in Heart failure; HELAS: Heart failure Long-term Antithrombotic Study.

We extracted detailed data about demographics, comorbidities, interventions, follow-up and outcomes. Data extraction and data entry into software was double-checked. Disagreements were resolved by consensus.

Quality reporting assessment

Quality of reporting was analysed by using a qualitative classification according to risk of bias (high, unclear or low risk), adapted from Cochrane Collaboration's Tool[15]. Studies were not excluded based on quality of reporting.

Statistical analysis

Outcomes data were summarized as frequencies. Statistical analyses were performed using the RevMan version 5.2.6 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) to derive forest plots with pooled estimates of risk ratios (RR) and their 95%CI. Statistical heterogeneity was assessed with χ^2 test and quantified with Higgins I^2 test[16]. Pooled results estimates were based on the random or fixed effects model according to the existence ($I^2 \geqslant 50\%$) or not ($I^2 < 50\%$) of significant heterogeneity[17]. Publication bias was assessed through visual inspection of funnel plots symmetry and Peters' regression tests[18,19]. Pooled results were evaluated for the overall antithrombotic treatment, as well separately for antiplatelet and anticoagulation groups.

RESULTS

Search

After title and abstract screening of citations obtained in Medline and Cochrane Library, 196 citations were retrieved. One-hundred and eighty seven studies did not meet inclusion criteria through initial assessment: 107 included AF patients; 56 studies were not randomized and 24 did not address the pretended topic (either different population and/or other interventions).

The remaining 9 studies were fully-evaluated, of which 7 were further excluded: 5 were observational studies, and 2 RCTs did not include a placebo, standard care or no antithrombotic treatment arm (WARCEF and WATCH trials)[5,20]. Therefore, 2 RCTs were eligible for the purpose of this systematic review[21,22]. The search of reference lists of review articles and included studies failed to identify any additional eligible study[23-27]. Figure 1 shows the flowchart of studies' selection.

Characteristics of obtained studies and quality of reporting

Studies Warfarin/Aspirin Study in Heart failure (WASH) and Heart failure Long-term Antithrombotic Study (HELAS) met the outlined inclusion criteria[21,22].

WASH study was an open-label RCT with blinded endpoint assessment, published in 2004. WASH enrolled 254 patients (80 warfarin; 80 ASA; 94 no anti-thrombotic treatment) with CHF and sinus rhythm and followed them for a mean period of 2.25 years. About 60% had CHF of ischemic etiology, 75% of the patients were male, mean age was 63 years old, and 30% were in New York Heart Association class Ⅲ/Ⅵ. About 34% of the patients had hypertension, and 20% had diabetes. In terms of echocardiography mean parameters, patients had a fractional shortening of 15% and a left-ventricular end-diastolic diameter of 66 mm. Regarding treatments, the daily dosage of acetylsalicylic acid was 300 mg and international normalized ratio (INR) target for warfarin-treated patients was 2.5 (range 2-3). Primary outcome was the composite of all-cause death, non-fatal myocardial infarction, or non-fatal stroke[21].

HELAS study was published in 2006 and included two comparisons: warfarin *vs* acetylsalicylic acid in patients with CHF of ischemic etiology (not evaluated in this review due to absence of a placebo/no treatment control arm); and warfarin *vs* placebo in 82 patients (38 *vs* 44) with dilated non-ischemic CHF in sinus rhythm. Study's mean follow was 1.8 years. Most of the patients were male and mean age was 55 years. Hypertension was present in 25% of the patients, and diabetes in 11%. No significant differences were noticed in the main baseline characteristics. Echocardiographic features of these patients were remarkable for a baseline ejection fraction of 28%, left ventricle end-systolic diameter of 58 mm and end-diastolic diameter of 70 mm. Target INR for warfarin treatment was 2-3. Primary outcome was the composite of all-cause mortality, non-fatal stroke, non-fatal myocardial infarction, peripheral or pulmonary embolism, hospitalisation, or HF worsening[22].

Quality of reporting assessment is available in Figure 2. The main methodological flaws were the open-label design of WASH and the unknown method of allocation concealment in HELAS.

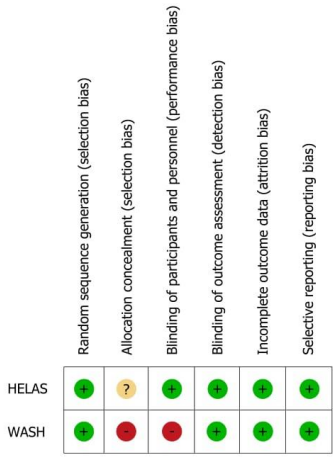

Figure 2 Studies quality of reporting. WASH: Warfarin/Aspirin Study in Heart failure; HELAS: Heart failure Long-term Antithrombotic Study.

Quantitative evaluation

Meta-analysis was performed for the following comparisons: antiplatelet drugs *vs* control, anticoagulant drugs *vs* control, and antithrombotic drugs (antiplatelet plus anticoagulant drugs) *vs* control.

While anticoagulation *vs* control data was derived from both WASH and HELAS studies[21,22], WASH study was the only that provided data for antiplatelet (acetylsalicylic acid) *vs* placebo[21]. For quantitative evaluation of overall antithrombotic treatment in this population, we considered both oral anticoagulation and antiplatelet from WASH study as a single arm and efficacy was directly obtained from WASH study[21].

Primary outcome

Antithrombotic drugs did not reduce stroke risk against placebo or no treatment, with RR = 1.18 (95%CI: 0.17-8.15) for antiplatelet drugs, RR = 0.30 (95%CI: 0.03-2.65) for anticoagulants, and RR = 0.52 (95%CI: 0.10-2.74) for overall antithrombotic drugs.

Secondary outcomes

Antithrombotic drugs showed an increased risk of CHF worsening (RR = 1.61, 95%CI: 1.04-2.48), mainly due to the single antiplatelet drug studied, acetylsalicylic acid, which had RR = 1.78 (95%CI: 1.08-2.92), while oral anticoagulants were not different from controls (RR = 1.03, 95%CI: 0.61-1.75).

Warfarin showed a significant increased risk of major bleeding (RR = 9.00, 95%CI: 1.14-70.90) and acetylsalicylic acid showed a non-significant trend (RR = 3.26, 95%CI: 0.13-79.04). The RR for overall major bleeding risk with antithrombotic drugs was 6.99 (95%CI: 0.89-54.64).

None of the antithrombotic drugs or overall antithrombotic treatment showed reduction of mortality and myocardial infarction risk in patients with systolic HF and sinus rhythm.

Antiplatelet drug/acetylsalicylic acid, but not warfarin, showed increased risk of the composite outcome of mortality, stroke, myocardial infarction, and worsening HF, most probably due to the increased risk of CHF worsening. Statistical heterogeneity was present in the evaluation of mortality when comparing antithrombotic drugs with control (I^2 = 58%). Figure 3 shows the pooled results. Publication bias was not evaluated due to the scarcity of studies[28].

DISCUSSION

Our main findings were the lack of proven efficacy of antithrombotic treatments, in patients with systolic HF and sinus rhythm, in the risk reduction of clinically important outcomes such as stroke, mortality and myocardial infarction; moreover, warfarin is associated to a significant 9-fold increased risk of major bleeding; and acetylsalicylic acid was associated with increased risk of CHF worsening.

The spotlight of this theme looks for Warfarin *vs* Acetylsalicylic acid comparison. By conducting this systematic review, the authors aimed to move back to the original problem and ask the question of whether antithrombotic treatments are, in the first place, effective in the treatment of CHF with sinus rhythm. If we accept that RCTs are the unique type of clinical studies that can prove causality with a reasonable margin of error, our results show that these interventions still have to prove their efficacy in this population, knowing that they owe an important bleeding risk. Furthermore, our attempt to perform a bayesian mixed treatment comparison meta-analysis, with data from clopidogrel arm from WATCH study[20], and warfarin *vs* acetylsalicylic acid presented in multiple systematic reviews and meta-analyses, failed due to high inconsistency in the statistical analysis of the network (data not shown). Although this inconsistence strongly compromises the results of such exercise, it is worth to report that placebo had a high probability of being the best treatment option. This reinforces the need of further trials to elucidate whether these interventions do/do not interfere with the prognosis, rather than have contradictory signs.

Accordingly, the 2012 consensus document of the HF Association of the European Society of Cardiology (ESC) and the ESC Working Group on Thrombosis corroborates our conclusions[29]. This consensus document stated that warfarin and acetylsalicylic acid should not be routinely used for thromboprophylaxis in patients with systolic HF and sinus rhythm, in the absence of concomitant comorbidities with clear indications for anticoagulation (*e.g.*, AF) or acetylsalicylic acid (*e.g.*, documented coronary artery disease).

Safety concerns regarding acetylsalicylic acid and HF (in patients with previously optimized background therapy with drugs such as angiotensin-converting enzyme inhibitors) were previously mentioned[30-32]. However if we

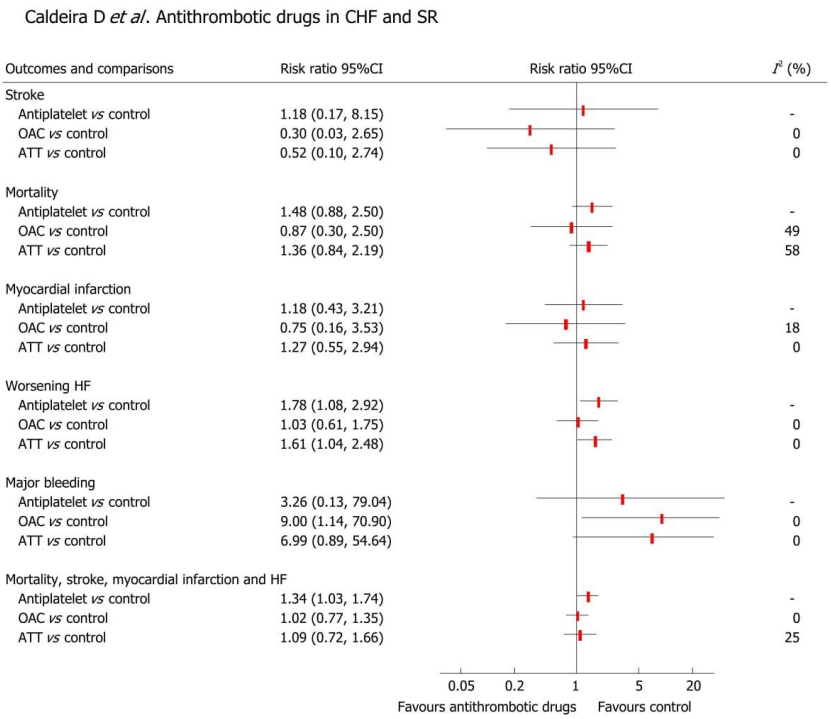

Figure 3 Forest plot evaluating antithrombotic drugs *vs* control. Data for "Antiplatelet *vs* control" comparison derived from WASH study. ATT: Antithrombotic treatment; OAC: Oral anticoagulation; HF: Heart failure; WASH: Warfarin/Aspirin Study in Heart failure.

consider warfarin as a "negative control", the pooled rates of HF worsening (after the WARCEF trial) were similar between acetylsalicylic acid and warfarin[7].

Along this century, antithrombotic treatment has gone forward in many therapeutic indications, but in patients with systolic HF and sinus rhythm the evidence to determine the prognostic importance of antithrombotic treatment (individually or globally) remained stationary and unsatisfactory for those who have to deal with CHF patients with sinus rhythm.

Limitations

This systematic review with meta-analysis has limitations attributed to included studies and analysis method.

As for included studies, WASH study had an open-label design; the control arm of this study was a no-antithrombotic treatment group (*i.e.*, not a placebo controlled trial), and included 7% of patients with AF that could not be excluded in the analyses. Furthermore the dosage of acetylsalicylic acid used in this trial was considerably higher than recommended[33].

Both studies had different proportions of HF etiologies. Although it can be important, particularly in ischemic HF cases where acetylsalicylic acid may play recognized prognostic role, here we aimed evaluate the thrombotic and embolic risk of patients with clinically important left ventricle impairment.

Major bleeding definitions were not common along the included trials. Worsening HF was defined by the investigator in WASH and no definition was provided in HELAS.

Periods of unrecognized paroxysmal AF could have biased of results. However it would bias favouring the antithrombotic drugs, which did not occur.

In conclusions, current evidence does not support the routine use of antithrombotic drugs (anticoagulant or antiplatelet drugs) for thromboprophylaxis in patients with systolic HF and sinus rhythm, as it carries a well known and documented bleeding risk without proven benefits compared to placebo or no antithrombotic treatment.

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COMMENTS

Background

In patients with atrial fibrillation (AF), chronic heart failure (CHF) increases

thromboembolic risk and oral anticoagulation is essential to decrease the risk of thromboembolic complications. Evidence suggests a positive association between CHF, impaired hemostasis and thromboembolic events. Whether antithrombotic drugs have an prognosis impact in patients with CHF in sinus rhythm (*i.e.*, without history of AF) is still very debated.

Research frontiers

Anticoagulation has been established as the gold standard treatment of stroke and embolism prevention in AF. The WARCEF trial did not show differences between warfarin and acetylsalicylic acid concerning major cardiovascular events in patients with CHF and sinus rhythm. Warfarin reduced the risk of ischemic stroke in this trial. However the efficacy of any of these drugs compared should be evaluated before drawing any conclusions and recommendations.

Innovations and breakthroughs

Based on the best available evidence (2 randomized controlled trials Warfarin/Aspirin Study in Heart failure and Heart failure Long-term Antithrombotic Study), this systematic review emphasizes the lack of efficacy of any antithrombotic drugs (individually or pooled together) in patients with CHF and sinus rhythm. In addition should be considered that these drugs increase significantly the risk of major bleeding.

Applications

Warfarin and acetylsalicylic acid should not be routinely used for thromboprophylaxis in patients with systolic HF and sinus rhythm, in the absence of concomitant comorbidities with clear indications for anticoagulation (*e.g.*, AF) or acetylsalicylic acid (*e.g.*, documented coronary artery disease).

Peer review

A systematic review and meta-analysis of two studies addressing antithrombotic drugs in patients with CHF and sinus rhythm. The manuscript is well written and adds new points to the discussion of anticoagulation.

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Systematic Review/Meta-analysis

Oral Anticoagulation for Pulmonary Arterial Hypertension: Systematic Review and Meta-analysis

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See editorial by Hatton and Ryan, pages xxx-xxx of this issue.

ABSTRACT

Background: Uncertainty exists about the benefit of oral anticoagulation in the treatment of pulmonary arterial hypertension (PAH), which is a lethal disease. We aimed to review and quantify the effect of oral anticoagulants in overall survival of PAH patients.

Methods: We searched for randomized and observational studies that evaluated oral anticoagulants in PAH in the electronic databases MEDLINE, CENTRAL and ISI Web of Knowledge (December 2013). Review articles and references were also screened. We performed a random effects meta-analysis to estimate pooled HRs and 95% confidence intervals. Statistical heterogeneity was evaluated using the I^2 test.

Results: No randomized controlled trials were identified. Nine cohort studies (2 prospective and 7 retrospective) of overall moderate quality that enrolled 1730 PAH patients were included. Oral anticoagulation (warfarin) was associated with a 31% mortality risk reduction (HR,

RÉSUMÉ

Introduction : Les avantages de l'anticoagulation par voie orale dans le traitement de l'hypertension artérielle pulmonaire (HAP), une maladie mortelle, sont incertains. Notre but était de passer en revue et de quantifier l'effet des anticoagulants par voie orale sur la survie globale des patients souffrant d'HAP.

Méthodes : Nous avons examiné des études aléatoires et observationnelles provenant des banques de données MEDLINE, CENTRAL et ISI Web of Knowledge (décembre 2013) qui évaluaient les anticoagulants par voie orale utilisés contre l'HAP. Les articles de revues et les bibliographies ont également été examinés. Nous avons réalisé une méta-analyse à effets aléatoires pour estimer les rapports de risque (RR) globaux et les intervalles de confiance à 95 %. L'hétérogénéité statistique a été évaluée par le test I^2.

Résultats : Aucun essai clinique aléatoire n'a été considéré. Neuf (9) études de cohortes (2 prospectives et 7 rétrospectives) de qualité

Pulmonary hypertension (PH) is a clinical entity defined as mean pulmonary artery pressure $\geq$ 25 mm Hg at rest measured using right heart catheterization.[1] According to the Dana Point classification there are 5 aetiologic groups for PH: PAH; PH due to left heart diseases; PH associated with pulmonary diseases or hypoxia; chronic thromboembolic PH; and PH with unclear and/or multifactorial mechanisms.[2]

PAH corresponds to Dana Point group 1 and includes idiopathic and heritable forms of the disease, PAH associated with drugs and toxins, and associated forms of PAH. The landmarks of pathological findings are vascular proliferation and remodelling of the small pulmonary arteries, accompanied by in situ thrombosis.

Based on observational studies and/or post hoc analyses of clinical trials, the European Society of Cardiology and the European Respiratory Society guidelines recommend oral anticoagulation for patients with idiopathic PAH, heritable PAH, and anorexigen-induced PAH (class IIa recommendation), and also for patients with associated forms of PAH (class IIb recommendation).[1]

The benefit of oral anticoagulation for PAH has been previously evaluated in a systematic review published in 2006.[3] However, the authors of this systematic review did not

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0.69; 95% confidence interval, 0.57-0.82; $I^2 = 28\%$). Subgroup and sensitivity analyses showed similar results and no significant heterogeneity.

Conclusions: There is no randomized evidence to support the use of oral anticoagulation in PAH. Pooled results from cohort studies suggest a survival benefit, but the moderate study quality, the high risk of publication bias, and the methodological limitations inherent in the analysis of observational studies preclude a definite conclusion. There is an urgent need for pragmatic randomized evidence to definitely answer this important clinical question.

globale modérée qui totalisaient 1730 patients souffrant d'HAP ont été retenues. L'anticoagulation par voie orale (warfarine) a été associée à une réduction du risque de mortalité de 31 % (RR, 0,69; intervalle de confiance à 95 %, 0,57-0,82; $I^2 = 28$ %). Les analyses en sous-groupes et de sensibilité ont montré des résultats similaires et aucune hétérogénéité significative.

Conclusions : Il n'y a aucune donnée probante issue d'études aléatoires qui soutient l'utilisation de l'anticoagulation par voie orale pour traiter l'HAP. Les résultats regroupés des études de cohortes suggèrent un avantage de survie, mais les études de qualité modérée, le risque élevé de biais de publication et les limites méthodologiques inhérentes à l'analyse des études observationnelles empêchent de mener à une conclusion définitive. Il existe un besoin urgent de données probantes issues d'études aléatoires pragmatiques pour répondre de manière définitive à cette importante question clinique.

use quantitative methods to estimate the potential benefit (and harms). Furthermore, the uncertainty about the clinical benefit of oral anticoagulation in PH is reflected in the results of a recent PH expert opinion survey about anticoagulation benefit in patient survival.[4] Additionally, new studies, such as the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) registry,[5] have been published. In this context, we thought that a systematic review about the benefit of oral anticoagulation in PAH survival was necessary to better aid physicians in clinical decision-making. In this article, we present the results of such a study.

Methods

Meta-analysis **O**f **O**bservational **S**tudies in **E**pidemiology (MOOSE) statement guidelines were used as a reference for reporting data of this systematic review.[6]

Eligible studies

Randomized controlled trials or cohorts studies (whether prospective or retrospective) that evaluated oral anticoagulation in patients with PAH were selected.

Oral anticoagulation was defined as chronic treatment with warfarin, acenocoumarol, phenprocoumon, fluindione, dabigatran, rivaroxaban, or apixaban. Oral anticoagulation without definition of the specific drug was also accepted. Studies had to compare oral anticoagulation with placebo or no treatment.

Studies that met inclusion criteria were not excluded a priori based on weakness of design or data quality.

Information sources and search process

Investigators retrieved potential eligible studies using an electronic search in MEDLINE, CENTRAL (Cochrane Library), and ISI Web of Knowledge (with Conference Proceedings) databases, from inception to December 2013. Search strategy for MEDLINE (*MEDLINE search strategy [December 2013]* section of the Supplementary Material) included free-text words and Medical Subjects Headings terms without language restrictions to increase sensitivity. We also screened the reference lists of identified reviews and studies.

Data extraction, evaluation, and synthesis

Titles and abstracts of obtained records were independently screened and evaluated by 2 authors. Disagreements were solved by consensus. Selected studies were assessed using full text to determine their appropriateness for inclusion. Study characteristics and results were independently extracted into a standardized form. The primary outcome was mortality.

The chosen effect estimate was hazard ratio (HR) because relative estimates, such as risk ratio or HR, are more similar across studies with different designs, populations, and lengths of follow-up than absolute measures.[7] In addition, HR gives an estimate of treatment effect over time, which is particularly important in the case of PH because its carries a very high mortality rate in a short period of time.[8]

Reported quality of the studies was independently assessed by the 2 same authors using a qualitative classification according to risk of bias (high, unclear, or low risk). We planned to assess the risk of bias in randomized trials with the Cochrane Collaboration domain-based tool.[9]

The risk of bias in observational studies was assessed using 2 methods: (1) a 6-item classification system based on MOOSE, **Q**uality **A**ssessment **T**ool for **S**ystematic Reviews of **O**bservational Studies (QATSO), and **St**rengthening the **R**eporting of **Ob**servational Studies in **E**pidemiology (STROBE) adapted from previous published quality assessment instruments[6,10-13]; and (2) the Newcastle-Ottawa Scale for cohort studies.[14]

The following items were taken into consideration and had the same weight in the 6-item classification: (1) participants, if the population was adequate by reporting PH diagnosis using right heart catheterization; (2) participants, if the study had a representative sample of PAH patients (mostly female patients and with mean age of 35-65 years; most representative cohorts/registries have mean age approximately 50 years with standard deviations of 10-15 years)[15-17]; (3) exposure, if anticoagulant treatment was adequately assessed by investigators; (4) outcome; we considered studies to have a low detection bias if mortality was evaluated as a predefined outcome because of the nature of such a hard end point; (5) specific outcome adjustments, for at least 1 of the parameters with established importance for PAH prognosis: clinical evidence of right ventricle failure, rate of progression of symptoms, syncope, functional class, 6-minute walk test result, cardiopulmonary

exercise testing, natriuretic peptides, tricuspid annular plane systolic excursion, presence of pericardial effusion, right atrium pressure or cardiac index[18]; and (6) any other adjustments.

The Newcastle-Ottawa Scale uses 3 parameters related to methodology: patient selection (4 items), comparability of study groups (2 items), and assessment of outcome (3 items).[14]

Data analysis

We used IBM SPSS Statistics version 20 and RevMan 5.1.7 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) for statistical analysis. Weighted inverse-variance meta-analysis was performed to estimate pooled HRs and 95% confidence intervals (CIs).

For the purpose of analysis, when individual studies did not provide HR, we calculated this from provided raw data or survival curves using methods previously published.[19,20] These methods can provide more than 1 estimate according to input data. The authors were always conservative by considering for pooled analysis the estimate nearer to HR = 1.

A random effects model was used independently of the existence or not of statistical heterogeneity because we allowed combination of studies with different designs. Statistical heterogeneity was evaluated using the Higgins I^2 test, which measures the percentage of total variation between studies due to heterogeneity.[21-23] Publication bias was assessed using visual inspection of funnel plot asymmetry, Egger, and Peters regression tests.[24,25]

Results

Study selection

After searching electronic databases and references of obtained studies, we were able to include 9 cohort studies in this systematic review.[5,26-33] No randomized controlled trial that evaluated oral anticoagulants in PAH was identified. The search of the reference lists of review articles and included studies did not retrieve any additional study.[3,34-36] The flow chart of study selection is shown in Supplemental Figure S1, and Table 1 summarizes their main characteristics.

Global description of studies

Nine cohort studies (2 prospective,[28,33] and 7 retrospective[5,26,27,29-32]) were included. Cohort studies were published between 1966 and 2013 and all included patients with PAH corresponding to group 1 of the Dana Point classification: primary PH,[5,26,27,29] anorexigen-induced PAH,[30,32] and connective tissue disease.[33] The number of patients included was 1730 and ranged from 17 to 800 (median, 94; interquartile range, 65-117) in the individual studies. The mean/median patient age ranged from 32.5 to 68 years. Approximately 73% of the patients were female. Mean follow-up ranged from 2.5 to 14 years. Vitamin K antagonists (VKAs) were the most frequently used anticoagulants. Most studies reported unadjusted estimates, except 3 that provided outcomes adjusted for multiple variables. HR data were not available from the study of Storstein et al.[26] In this case, we assumed a proportional HR model with constant risk ratio for mortality. This measure was derived from raw data analysis.

Study quality assessments are shown in Supplemental Figures S2 and S3. Overall, the quality of cohort studies was moderate. The main methodological caveats were: (1) lack of adjustment of estimates to main prognostic variables; and (2) lack of cohort representativity. Older studies included younger patients, which does not reflect the patients of contemporary cohorts.[15-17]

Primary outcome: mortality

Pooled analysis of cohort studies showed a 31% decrease in mortality risk (HR, 0.69; 95% CI, 0.57-0.82; Fig. 1) among patients with PAH treated with VKAs (warfarin). Heterogeneity among studies results was low to moderate ($I^2 = 28\%$).

Sensitivity analysis

In the study published by Ogata and colleagues, 7 patients treated with warfarin and a vasodilator (nifedipine or isoproterenol) were compared with a group of 13 patients who did not receive anticoagulant or vasodilator treatment.[29] The retrieved effect estimate does not dissociate and might include a prognostic effect of vasodilators. Therefore, we performed a sensitivity analysis excluding this study. The obtained HR was 0.70 (95% CI, 0.58-0.84) with $I^2 = 29\%$. A sensitivity analysis excluding the study by Storstein et al.,[26] which does not provide HR data, produced similar results (HR, 0.67; 95% CI, 0.55-0.83; $I^2 = 36\%$).

To further explore the influence of PH patient characteristics in the retrieved estimates, we analyzed data excluding studies that evaluated patients with drug-induced PAH or connective tissue disease-associated PAH. Pooled results from studies that evaluated only patients with idiopathic PH (primary PH) also showed a significant decrease of mortality risk (HR, 0.75; 95% CI, 0.65-0.87; $I^2 = 7\%$) (Supplemental Fig. S4).

Analysis according to study design

Although heterogeneity of the pooled estimate was relatively low ($I^2 = 28\%$), we performed a subgroup analysis to explore how study design (prospective vs retrospective) influenced the results. In both designs, oral anticoagulation decreased the mortality risk compared with control, however, prospective studies showed greater risk reduction (HR, 0.32; 95% CI, 0.15-0.65) compared with retrospective (HR, 0.75; 95% CI, 0.66-0.86) studies ($P = 0.02$), all estimates without statistical heterogeneity ($I^2 = 0\%$). Figure 2 shows the Forest plot of the analysis.

Publication bias

The shape of the funnel plot shows an asymmetrical tail in the left side of the plot (favouring oral anticoagulant treatment) and Egger ($P = 0.003$) and Peters ($P = 0.02$) tests suggest publication bias and small study effects (Fig. 3).

Discussion

This systematic review focused on the survival effect of oral anticoagulation in patients with PAH.

PAH is still a lethal disease with high mortality rates. The National Institutes of Health Registry showed that the median survival from diagnosis was 2.8 years.[37] Other cohort studies

Table 1. Main characteristics of included studies

Reference	Study design	Patients/PAH population	Exclusion criteria	Age and sex	Functional class	Interventions	Follow-up	Primary outcome	Outcome adjustments
Storstein et al., 1966[26]	Retrospective cohort study	17 PPH patients	N/A	40.5 years; female, 59%	N/A	Anticoagulant vs no anticoagulant; 10 vs 7 patients	6 years	Mortality and hemodynamic parameters	None
Fuster et al., 1984[27]	Retrospective cohort study	115 PPH patients*	Thromboembolic episodes, deep venous thrombosis, COPD, valvular heart disease, primary intracardiac shunts, or CTD	34 years; female, 73%	N/A	Warfarin vs control; 78 vs 37 patients	Mean, 14 years	Mortality	None
Rich et al., 1992[28]	Prospective cohort study	64 PPH patients	N/A	36 years; female, N/A	N/A	Warfarin vs control; 35 vs 29 patients	5 years	All-cause mortality	None
Ogata et al., 1993[29]	Retrospective cohort study	20 PPH patients	N/A	Median, 32.5 years; female 70%	50% NYHA II and 50% NYHA III	Warfarin (with isoproterenol or nifedipine) vs control; 7 vs 13 patients	Mean, 7.6 years	Hemodynamic parameters	None
Frank et al., 1997[30]	Retrospective cohort study	173 PPH patients (n = 69) and anorexigen-induced pulmonary arterial hypertension (n = 104)	Pulmonary embolism, obstructive and restrictive lung disease, intracardial and extracardial shunt lesions, and cardiomyopathies	Mean 44 years; female, 83%	57% NYHA III and 31% NYHA IV	Warfarin vs control; 24 vs 45 (anorexigen PAH group) group; 56 vs 48 (PPH) patients	Mean 7.2 (anorexigen PAH) and 4 (PPH) years	Survival	None
Kawut et al., 2005[31]	Retrospective cohort study	84 patients: 66 idiopathic PAH, 14 familial and anorexigen-related PAH	Previous cardiac catheterization with acute vasodilator study and initiation of PAH therapy; other forms of PAH (eg, systemic sclerosis or SLE)	Mean, 42 years; female, 81%	N/A	Warfarin vs control; 79 vs 5 patients	Median 2.1 years	Death or lung transplantation	Multivariate
Saeed et al., 2011[32]	Retrospective cohort study	340 with PAH	Patients with heart or lung transplant	Mean 63 years; female, N/A	N/A	Warfarin vs control; 106 vs 234 patients	N/A	Survival	None
Ngian et al., 2012[33]	Prospective cohort study	117 patients with CTD-associated PAH: SSc, 84%; MCTD, 5%; SLE, 3%; RA, 3%	Patients with extensive interstitial lung disease	Mean 62 years; female, 90%	8% NYHA I; 12% NYHA II; 75% NYHA III; 5% NYHA IV	Warfarin vs control; 36 vs 81 patients	Mean 2.6 years	Survival	Multivariate
COMPERA Registry 2014[9]	Retrospective cohort study (idiopathic PAH cohort only)	800 patients with idiopathic PAH	—	Median 68 years (whole cohort); female, 64% (whole cohort)	13% NYHA I/II; 73% NYHA III; 14% NYHA IV (whole cohort)	Anticoagulant vs no anticoagulant; 528 vs 272	3 years	Mortality, transplantation, PAH-related hospitalization, deterioration of functional class, unscheduled change in PAH therapy, other serious adverse events	Multivariate

COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; MCTD, mixed connective tissue disease; N/A, not available; NYHA, New York Heart Association class; PAH, pulmonary arterial hypertension; PPH, primary pulmonary hypertension; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

Full cohort of Fuster's study was composed of 120 patients, but data about anticoagulation was available for 115 patients.

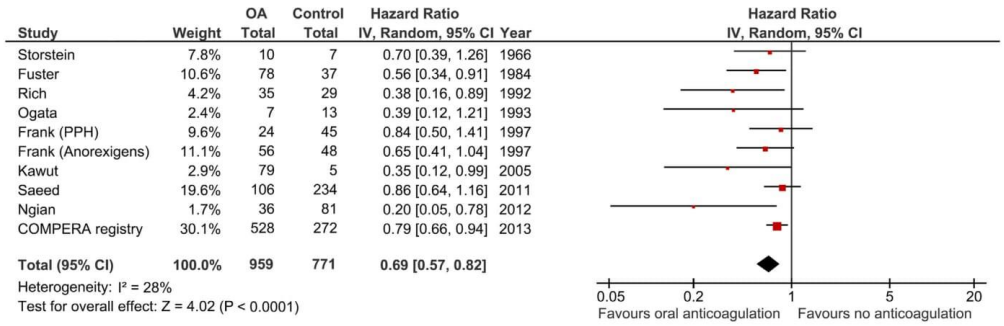

Figure 1. Overall survival: oral anticoagulation vs control. CI, confidence interval; COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; IV, inverse variance; OA, oral anticoagulation; PPH, primary pulmonary hypertension.

reported survival rates of approximately 85%-90% at 1 year, 33%-58% at 3 years of follow-up and > 50% at 5 years.[15-17,38,39]

In a systematic review, Galiè and colleagues found that drugs such as prostanoids, endothelin receptor antagonists, and phosphodiesterase type-5 inhibitors were associated with a 38% reduction of death risk in short-term randomized controlled trials (RCTs).[40] Data from placebo arms of RCTs included in this systematic review highlight the poor prognosis with mortality rates at 14 weeks reaching as high as 3.8%, about 1.1% per month.[40]

Similar to drugs evaluated by Galiè and colleagues, oral anticoagulants have also been claimed to be associated with increased survival in some PAH patients. The rationale for this intervention in PAH was described more than 60 years ago.[41] However, no randomized controlled trials have been conducted. European Society of Cardiology/European Respiratory Society PH guidelines recommend (recommendation class II) this treatment for patients with idiopathic PAH, heritable PAH, anorexigen-induced PAH, and associated forms of PAH.[1]

In the present systematic review, we quantitatively addressed the benefit of oral anticoagulation in terms of

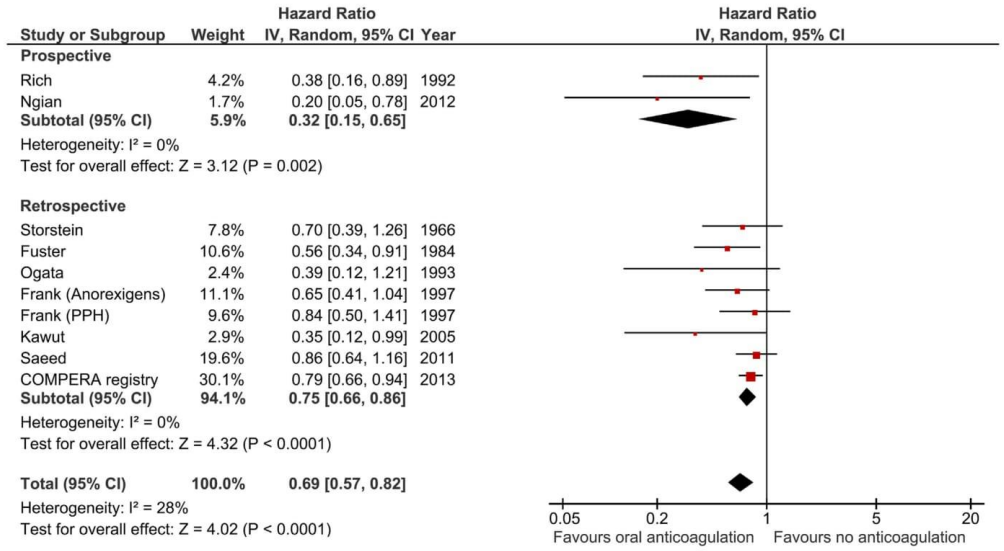

Figure 2. Forest plot with pooled analysis according to study design: prospective and retrospective cohorts. Subgroup differences ($P = 0.02$). CI, confidence interval; COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; IV, inverse variance; PPH, primary pulmonary hypertension.

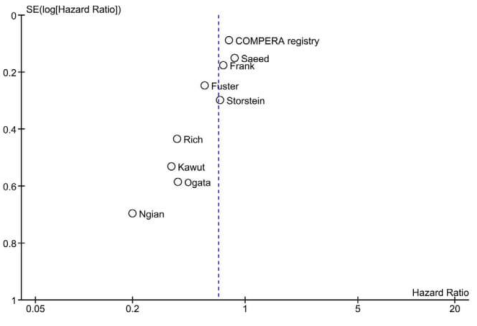

Figure 3. Funnel plot with included studies. COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; SE, standard error.

mortality in patients with PAH. No randomized controlled trials were identified and therefore our estimates are based on observational studies, which cannot prove causality, rather associations between an intervention and an outcome. Furthermore, the high risk of publication bias and the overall low to moderate quality of included cohorts, further limits the strength of the conclusions that can be made. We used as association measurement the HR, which is a time-linked measure that highlights efficacy in studies with high mortality rates. For the present analysis we assumed proportional HR principle that relies on constant event rates over time, despite that studies with shorter follow-up were those with the greater risk reduction.[31,33]

Compared with the previous review,[3] ours included more studies with a larger population. Additionally, we estimated the dimension of the effect of anticoagulation in prognosis of PAH patients. Our results suggest that oral anticoagulation has a positive effect on the natural history of PAH by reducing the relative risk of death in 31% over a period of time, compared with nontreated patients (HR, 0.69; 95% CI, 0.57-0.82). With the exception of the COMPERA registry, which included contemporary patients, 45% of them treated with combination therapy, most of the previous studies did not include patients with PAH-targeted therapy. In the absence of RCTs, this study provides the most robust data from a large population treated with the current standard of PAH treatment.

Performing meta-analysis using observational data raises methodological and interpretation concerns.[6] Clinical decisions based exclusively on this type of evidence should be weighed with caution. Nevertheless, these data are informative and increase the knowledge of interventions and diseases for a longer period, usually not assessed in randomized controlled trials.[42,43] In fact, there is growing empirical evidence that systematic reviews of harm should incorporate non-randomized rather than just randomized data.[44,45]

PAH pathophysiology relies on multifactorial mechanisms of disease. However, inflammation, vasoconstriction, and vascular thrombosis are hallmarks of PAH.

The focus on thrombotic burden in PAH is the result of the classical histopathological studies, in which thrombotic arterial disease in 40%-50% patients with PAH was found.[46,47] Basic and clinical studies reviewed by Johnson and colleagues support PAH as a prothrombotic state condition with increased activity of the coagulation pathway and impaired fibrinolysis.[36,48] Therefore, there is a rationale for treating PAH patients with anticoagulant drugs. Special attention should be paid to PAH aetiology and comorbidities for bleeding risk stratification and assessment of contraindications for anticoagulant treatment. For example, patients with porto-PH are high bleeding risk individuals because these patients have structural weaknesses in portosystemic anastomosis, namely esophageal varices, in addition to a possible impaired coagulation due to liver dysfunction. Anticoagulation is not recommended in this situation.

In treating patients with PAH, it is important to be aware of the interactions between VKA and PAH-specific treatments. Sildenafil use has been associated with increased prothrombin time due to the interference with cytochrome P450 (CYP)3A4 and CYP2C9, enzymes involved in VKA metabolism. Endothelin receptor antagonists also interfere with these CYPs. Anecdotal reports with bosentan highlight this interaction with an inhibitory effect of this drug over warfarin.[49,50] However, the most remarkable interference, with a trend for increased International Normalized Ratio and/or bleeding diathesis, appears to be related to sitaxsentan, an endothelin receptor antagonist which was withdrawn because of the increased risk of drug-induced liver injury.[51] Prostacyclin analogues might also interfere with bleeding risk. These drugs are associated with thrombocytopenia and abnormal platelet function.[52,53] In a Dutch study in which the safety of VKAs in patients with PH was evaluated, prostacyclines were found to represent a risk factor for major bleeding.[54]

To optimize the benefits of oral anticoagulation, it is important to closely monitor PAH patients especially when introducing or changing treatment.

A call for randomized controlled studies have been repetitively mentioned in previous studies.[3,4] As already mentioned, uncertainty exists among expert opinion and data interpretation about the effect of oral anticoagulation in the natural history of the disease.[4] Johnson and colleagues used the data from prior studies retrieved from expert opinion to calculate posterior probabilistic estimates of warfarin benefit in a matched PAH cohort.[4] According to this Bayesian exercise, warfarin was unlikely to improve survival in the era of PAH-specific treatments.[55] These results further highlight the need for properly powered RCTs in this condition. Additionally, new oral anticoagulants (anti-IIa or anti-Xa) might play a role in this subset of patients.

Limitations

This systematic review has limitations inherent in the included studies; their reporting quality and analysis methodology. The best available evidence on this topic is based only on observational studies (that primarily addressed idiopathic and drug-induced PAH), most of them without adequate baseline and/or outcome adjustments for main prognosis variables.

Inadequate representation of obtained studies was based on age because most of them included predominantly female patients. In the study of Ngian et al. we also considered it not to be representative because it included only a specific cluster of PAH.[33] The problem of age might be a reflection of

diagnosis and treatment evolution in PAH because average life expectancy in these patients has been significantly increased.[40] As expected, contemporary cohorts comprise older patients compared with older studies. We considered for analysis the Dana Point group 1 PH patients. This is still a heterogeneous group, posing some limitations on conclusions.

At the outcome level, 1 study included transplant in the survival outcome.[31] Despite that, the proportions of transplant patients was small: 1 in 25 patients reaching end point. The exclusion of this study did not change the direction and significance of the association oral anticoagulation-survival (data not shown). Considering the study published by Ogata et al.,[29] they compared a strategy of oral anticoagulation and vasodilators vs no anticoagulation/vasodilators. The vasodilator effect was not dissociable from anticoagulation in this study. To decrease bias added by this study, we performed a sensitivity analysis with results similar to those obtained in the main analysis.

The funnel plot, Egger, and Peters tests suggested publication bias. This means that smaller studies with an association between oral anticoagulant treatment and lack of survival benefit might not have been published. The scarcity of PAH survival-oral anticoagulation data could have contributed by chance to positivity of publication bias tests.

Although the heterogeneity of pooled results was relatively low and all studies shared the same directionality, meta-analysis of observational data is inherently flawed. In an attempts to partially counterbalance such limitations, when more than 1 estimate was available using our methodology, we opted for the most conservative, respecting the directionality and significance of the results.

Conclusions

The present systematic review did not identify any randomized controlled trial, and therefore no definitive causality can be established between oral anticoagulation and mortality risk among PAH patients. The best available evidence is based solely on observational studies that evaluated mostly VKAs. Pooled results from these studies suggest an association between oral anticoagulation and increase of overall survival in patients with PAH, particularly idiopathic PAH. The weakness of the data and the methodological limitations inherent in the analysis of observational studies preclude a definite answer to this important clinical question. To change this scenario of uncertainty, there is an urgent need for pragmatic randomized evidence.

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Supplementary Material

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Meta-Analysis

Safety of non-vitamin K antagonist oral anticoagulants - coronary risks

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Abstract

Introduction Since the approval and commercialization of non-vitamin K antagonist oral anticoagulants (NOACs; apixaban, dabigatran, edoxaban, and rivaroxaban) several studies and meta-analyses have raised safety concerns regarding myocardial infarction (MI) risk among NOAC-treated patients, particularly with dabigatran. Uncertainty remains regarding the coronary risk associated with dabigatran, and whether this putative risk also applies to the other NOACs.

Areas covered In this review, the coronary risks of NOACs based on findings from placebo-controlled trials are discussed, and randomized controlled trials and major cohort studies in AF patients are also appraised. We performed a random-effect meta-analysis, including both interventional trials and observational studies ("real-world" data). Further estimates were retrieved from the meta-analysis of coronary risk among NOAC-treated patients with concomitant AF and coronary disease.

Expert opinion Currently, the best available data from both clinical trials and observational studies do not support the claim that patients treated with NOACs, including dabigatran, are at increased coronary risk. However, a definitive conclusion cannot be made (especially regarding dabigatran) and further data are required to address the coronary risks, mostly of high-risk patients. As with any therapeutic intervention, the possible complications should be balanced against the potential benefits at an individual patient level.

Keywords: NOACs, DOACs, TSOACs, apixaban, dabigatran, edoxaban, rivaroxaban, myocardial infarction.

Abbreviations

ACS: Acute coronary syndrome

AF: Atrial fibrillation

CAD: Coronary artery disease

CI: Confidence interval

CV: Cardiovascular

HR: Hazard ratio

INR: International normalized ratio

MI: Myocardial infarction

NOACs: Non-vitamin K antagonists oral anticoagulants

OR: Odds ratio

PCI: Percutaneous coronary intervention

RCT: Randomized controlled trial

RR: Risk ratio

TTR: Time in therapeutic range

VKA: Vitamin K antagonist

VTE: Venous thromboembolism

Article Highlights

Some systematic reviews claimed for an increased risk of myocardial infarction associated with dabigatran.

Pooled data from clinical trials do not support the increased risk of acute coronary events associated with NOACs.

In patients with atrial fibrillation and coronary artery disease, the risk of coronary events associated with NOACs was not increased, including dabigatran.

Pooled data of observational studies does not support the claim of increased coronary risk among patients treated with dabigatran.

Ongoing trials will supply further data in order to address more powerfully the coronary risks, mostly in AF patients with coronary disease.

Coronary risks should be considered together with other efficacy and safety outcomes (stroke and major bleeding risk reduction)

1. Introduction

The new oral anticoagulants, also called non-vitamin K antagonist oral anticoagulants (NOACs)[1], direct oral anticoagulants (DOACs) or target-specific oral anticoagulants (TSOACs), exert their antithrombotic action by blocking the common pathway of the coagulation cascade, either on factor Xa or thrombin. These drugs were evaluated in different prothrombotic settings and performed, at least, as efficaciously as Vitamin K Antagonists (VKA) in patients with venous thromboembolism (VTE) or non-valvular atrial fibrillation (AF).[2, 3] Differently from VKA, NOACs do not require regular evaluations of laboratorial hemostatic parameters, and have a lower risk of major bleedings, bleeding-related case-fatalities and intracranial bleedings.[4, 5]

There are four approved NOACs: apixaban, dabigatran, edoxaban and rivaroxaban. Most of the patients suitable for treatment with NOACs have non-valvular AF. The main complication of AF is stroke and systemic embolism, but AF is also associated with an almost 2-fold increased risk of myocardial infarction (MI).[6] Some studies have raised safety concerns regarding MI risk among NOAC-treated patients, particularly with dabigatran.[7] As such, it remains largely unknown if an increased coronary risk associated with dabigatran truly exists (and how much is that risk across different patients subgroups), and if this putative risk also applies to the other NOACs.

In this expert review, we aimed to retrieve and discuss the available evidence through electronic literature systematic searches (including published systematic reviews on this field) in order to retrieve powered data about NOACs risk of acute coronary events (unstable angina [UA] or MI) and cardiovascular mortality.

We evaluated NOACs coronary risk (ACE) reported in randomized placebo-controlled trials (RCTs). NOACs risk in AF patients were also discussed, with a particular focus on the high-risk subgroup of patients with both AF and coronary artery disease (CAD). Although RCTs are the gold standard methodology to establish cause-effect

relationship, they are frequently unpowered to address safety issues, in particular unfrequently adverse events and adverse events that occur late in time.[8-10] Therefore, we also considered data from post-marketing setting (observational studies) as a proxy of 'real-world' data.

2. Methodology

This review aimed to retrieve the best available evidence from key topics about the safety of NOACs regarding coronary events. A systematic search for acute coronary events amongst NOACs (apixaban, dabigatran, edoxaban, rivaroxaban) studies was performed in October 2015 through a comprehensive literature search in MEDLINE and Cochrane Library.

First we looked for ACS and cardiovascular death risk in placebo-controlled trials with NOACs (Section 3). Secondly, AF trials were appraised for NOACs ACS and CV death risk, with a pooled analysis including VKA-controlled trials. A subgroup analysis of patients with AF and history of CAD or MI was also performed (Section 4). In section 5, VKA-controlled observational longitudinal data of NOACs was pooled in order to retrieve ACS risk estimate among 'real world' patients. Section 6 summarizes the available systematic reviews about ACS risk and NOACs.

Meta-analysis was performed to retrieve global estimates along sections 3 to 5. RevMan 5.3.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for statistical analysis and to derive forest plot showing the results of individual studies and pooled analysis.

NOACs were compared with placebo or VKA (through random effects meta-analysis to estimate pooled risk ratio (RR) or hazard ratio (HR) and their 95% confidence intervals (95% CI). Whenever possible, only the approved doses of NOACs were considered for analysis. When raw data were available the results were calculated and expressed as

RR. When data estimates (HR) were adjusted to confounding factor the metric was preserved. Estimates for different doses were merged into a single one through random effects meta-analysis.

Heterogeneity measured as the percentage of total variation between studies due to heterogeneity was assessed through the I^2 test[11].

3. NOACs and acute coronary events in VTE and ACS placebo-controlled trials

A systematic search of placebo-controlled trials retrieved 3 RCTS in patients potentially eligible for an extended anticoagulation period following VTE (i.e. secondary prevention, not acute treatment),[12-14] and 6 RCTs in patients with acute coronary syndromes (ACS), without AF, receiving standard antiplatelet therapy (Table 1).[15-20]

Regarding the coronary risk among 5013 with a previous episode of VTE patients challenged with NOACs or placebo (for secondary prevention), the random effects pooled analysis with approved doses of NOACs did not show an increased risk of incident ACS (Risk ratio [RR] 0.93; 95% Confidence Interval [CI] 0.33 to 2.67; Heterogeneity [I^2]: 0%) (Figure 1). No difference was found among estimates for the different NOACs.

Six placebo-controlled RCTs (4 phase II RCTs and 2 Phase III RCTs) evaluating the add-on value of NOACs on top of standard antiplatelet treatment reported data for acute coronary events in patients with recent ACS. The APPRAISE studies assessed Apixaban,[15-17] the ATLAS studies assessed Rivaroxaban,[18, 19] and the RE-DEEM study assessed dabigatran.[20] Overall, these RCTs included a total of 23313 ACS patients. Seeing that phase II studies employed doses not approved, for this random effects pooled estimate we have only used data from studies evaluating approved doses of NOACs. In the ATLAS ACS2-TIMI 51 study, the dose for event reduction in ACS was 2.5 mg twice daily,[18] which is much lower than the doses currently approved for

thromboembolic prevention in patients with non-valvular AF, and that were used in the remaining placebo-controlled ACS trials.

Overall, random effects pooled analysis did not show a significant increase of the risk of MI (low heterogeneity among study results), severe recurrent ischemia or cardiovascular (CV) death (moderate heterogeneity among study results) with NOACs (Figure 2).

It is worth noting that all NOACs, with exception of dabigatran, showed a trend towards a decrease risk of MI. However, coronary risks should not be appraised using solely MI as outcome, but rather having an integrative view of cardiovascular, including cardiovascular mortality. Considering this, dabigatran was not associated with an increased risk of cardiovascular mortality or overall cardiovascular events.

4. NOACs and acute coronary events in patients with non-valvular AF RCTs

Our systematic search for acute coronary events data in non-valvular AF trials retrieved 7 RCTs (Table 2): one RCT comparing apixaban with acetylsalycilic acid (ASA),[21] and 6 RCTs comparing NOACs with VKA.[22-27] Studies such as ARISTOTLE-J and PETRO were not included in the analysis because these were unremarkable for acute coronary events with NOACs approved doses.[28, 29]

The AVERROES study compared apixaban with ASA in 5599 patients with non-valvular AF deemed to be unsuitable for VKA treatment by their physicians.[21] This study was prematurely halted due to the beneficial effects of apixaban in the reduction of stroke or systemic embolism events without significantly increasing the risk of major bleeding. Regarding MI risk, the yearly rates were very similar with 0.8% for apixaban and 0.9% for ASA (Hazard Ratio [HR] 0.86, 95%CI 0.50-1.48). Cardiovascular mortality risk was also similar between apixaban and ASA (HR 0.87, 95%CI 0.65-1.17).[21]

Regarding VKA-controlled trials, it is important to stress that VKA is an effective drug in the prevention of coronary events.[30, 31] However, its efficacy and safety are strongly dependent on the time in therapeutic range (i.e., the percentage of time that patients have a 'protective' International Normalized Ratio (INR)). The pivotal trials for NOACs approval had different median time in therapeutic range (TTR) and follow-ups. Due to the potential impact of VKA control in MI risk we attempted to perform a linear regression between NOACs RR and incidence of MI in VKA arm, with median time in therapeutic range. Data shows a decrease of MI events in VKA arm with higher TTR and a higher RR for MI (Figure 3). Therefore it is acceptable to consider anticoagulation control as a potential bias in the interpretation of NOACs coronary risk data (Figure 3).

Even though the data retrieved from 6 RCTs (74358 patients) showed that MI risk was not increased with NOACs use (RR 0.99; 95%CI: 0.84 to 1.18; I^2: 34%), similarly as occurred when overall ACS (MI plus UA) risk was appraised (RR 0.93; 95%CI: 0.79 to 1.09; I^2: 20%).

Individually, apixaban and rivaroxaban were not associated with increased coronary risk, while findings for dabigatran show a non-significant increase of MI risk (RR 1.26; 95%CI: 0.94 to 1.28), which was not dose-dependent (RR 1.32 [0.95 to 1.84] for 110mg and RR 1.30 [0.93 to 1.81] for 150mg). However when data from this trial were merged and analyzed together with other cardiac ischemic events, such as UA, revascularization and cardiac death, this putative risks seem to fade out.

Random effects pooled analysis did not show increased risk of MI, ACS or cardiovascular death with NOACs (Figure 4).

Subgroup of patients with AF and history of MI/CAD

RE-LY, ROCKET AF and ARISTOTLE provided insights about the subgroup of patients with previous CAD/MI. [32-34] ROCKET AF population had a high risk for thromboembolic

events. Patients with history of coronary disease had a higher thromboembolic risk score compared to those without CAD history (CHA_2DS_2-VASc 3.64 vs. 3.43).[32] Despite the significance of the difference found, this did not translate into higher rates of stroke and systemic embolism. Nevertheless, the incidence of MI and cardiovascular mortality was significantly higher in this CAD population. All these finding were also seen in the ARISTOTLE trial[33].

ARISTOTLE included 6639 patients with CAD, ROCKET AF enrolled 2468 patients with MI history, and RE-LY had 7039 patients with MI or CAD history. Overall, a total of 16146 patients with both AF and CAD were evaluated in these trials. Pooled results (Figure 5) failed to show an increase risk of incident MI with NOACs among these high-risk patients (HR 1.10; 95%CI: 0.90 to 1.34; I^2: 6%). No differences were found among estimates for the different NOACs.

5. 'Real-world' data about NOACs and coronary risks

Dabigatran was the first NOAC to be commercially available and, as far as the authors are aware, published 'real-world' observational data for coronary risks are only available for this NOAC. At our best knowledge there are also no pooled data about NOACs coronary risks compared to VKA (or other comparator) in the post-marketing setting. Nevertheless the data from the single-arm observational study with rivaroxaban, XANTUS, shows an incidence rate of 4 myocardial infarctions per 100 patient-years, while stroke occurred in 0.7 rivaroxaban-treated individuals per 100 patient-years.[35]

We calculated the pooled estimate of MI risk using adjusted data from 5 observational cohort studies (3 prospective studies[36-38] and 2 retrospective studies[39, 40]) evaluating a total of 208879 AF patients (Table 3). Dabigatran was not associated with an increased risk of MI in comparison to VKA (HR 0.96; 95% CI: 0.83 to 1.11; I^2: 68%). Recognizing the methodological drawbacks of observational studies, in comparison to exploratory

clinical trials, observational studies provide relevant information about efficiency and safety of drugs in a clinical context closest to every-day practice.[41] Therefore, it is also important to consider this information in the process of clinical decision making.

6. Other systematic reviews/meta-analysis

The risk of coronary events, particularly MI, has been previously debated in systematic reviews and meta-analysis (Table 4).[7, 41-48] In these systematic reviews and meta-analysis, most of the data weight derived from AF and VKA-controlled trials.

Apixaban was not associated with an increased risk of MI or CV death in meta-analyses that pooled data from different conditions and comparators.[41, 42] Using the same methodology, rivaroxaban was found to be associated with a significant MI and CV death risk reduction.[45, 48]

Dabigatran's increased risk of MI was highlighted in three systematic reviews with meta-analysis.[7, 43, 44] The MI odds ratio in comparison to other drugs ranged from 1.33 to 1.42. Despite that, all reviews were consistent in concluding that dabigatran did not increase the risk of CV or all-cause mortality. In fact, some reviews reported a significant mortality risk reduction with dabigatran.[7, 44]

In the absence of head-to-head trials, Loke et al. performed a systematic review assessing NOACs coronary risks through adjusted indirect treatment comparisons meta-analysis.[46] Using VKA as the common comparator, they concluded that dabigatran had an increased risk of ACS compared to rivaroxaban or apixaban. Although data are informative it is important to emphasize that the analysis was very focused on coronary events and held some limitations.[49]

Oldgren stated that the addition of (overall) NOACs to standard antiplatelet therapy in patients with ACS, results in a modest reduction in cardiovascular events but a substantial increase in bleeding risk, particularly in those treated with dual antiplatelet therapy.[47]

7. Expert opinion

The NOACs have changed the therapeutic landscape of oral anticoagulation overcoming some limitations of VKAs. As occurs with any new class of drugs, their safety requires a comprehensive evaluation not only before but also after marketing. RCTs and observational studies are both informative to evaluate safety. There is no evidence for a harmful class effect of NOACs regarding the risk of acute coronary events. However, dabigatran has been associated with a significant increased risk of MI in some systematic reviews including RCTs.[7, 44]

In placebo controlled trials, none of NOACs was associated with an increase coronary risks. In fact, the addition of these anticoagulants on top of standard antiplatelet therapy, increased bleeding risk across all NOACs in a dose-dependent manner outweighing the potential antithrombotic benefits. Only rivaroxaban 2.5 mg bid (a daily dose 66% to 75% lower than the doses approved for non-valvular AF) appeared to reduce the overall cardiovascular risk in patients with ACS without AF.[18] In this RCT an increase of bleeding risk was also reported but those findings were not detrimental for regulators to approve this dose.[18] In the placebo-controlled trials RE-SONATE and RE-DEEM,[13, 20] dabigatran did not increase the risk of MI. Moreover, the results for the approved dabigatran doses (110 mg and 150 mg) in the RE-DEEM trial reduced the risk of major adverse cardiovascular events and showed a trend towards lower cardiovascular mortality in patients with ACS.

RE-LY trials has shown a trend towards an increase of MI, however a post-hoc analysis after events readjudication showed an increase in the risk of acute coronary events among dabigatran treated patients was not significant.[34] Looking even closer to RE-LY data, UA and cardiovascular mortality were also recorded in order to capture more broadly myocardial/acute coronary events. In patients with non-valvular AF enrolled in the RE-LY trial, dabigatran showed a trend to increase the risk of MI. However, when UA, revascularization (percutaneous coronary intervention or coronary

artery bypass graft surgery) or cardiac deaths were evaluated, their risks were not significantly different between dabigatran and warfarin treatment groups.[34] When looking at overall ACS events (by adding UA to MI data), dabigatran had numerically less ACS events compared with warfarin.

Another dabigatran trial that also generated some coronary concerns was the RE-MEDY trial.[13] This study compared dabigatran with VKA in patients with VTE (which excluded from the main analyses of this review). There were 13 ACS with dabigatran and 3 events with VKA (p = 0.02).[13] Dabigatran arm had a higher proportion of diabetic patients and this imbalance in an important risk factor for CAD could have biased the data.

In the present review, we have further complemented AF data by performing a pooled analysis of adjusted MI risks in non-valvular AF patients at high risk (previous history of CAD or MI) of coronary events included in RCTs, as well as a meta-analysis of observational studies. In both analyses dabigatran was not associated with an increased risk of ACS events. However, it is worth noting that in some observational studies MI occurred more frequently with dabigatran (in comparison to VKA) among men and VKA-experienced subgroups of patients.[36, 37]

Dabigatran selectively targets thrombin (factor IIa), while rivaroxaban, apixaban and edoxaban block factor Xa. This difference prompted for possible explanatory links relating the local of coagulation blockade to the potential risk of coronary events.[50] The major drawback of this hypothesis relies on the absence of increased risk of overall ischemic events in RCTs evaluating bivalirudin (a parenteral thrombin inhibitor) in patients with ACS undergoing percutaneous coronary intervention.[51-53] In fact, bivalirudin is an anticoagulant of reference in patients requiring primary percutaneous coronary intervention (PCI).[54] There are also no obvious reasons for oral thrombin inhibitors to be harm compared to parenteral thrombin inhibitors. Therefore it is unlikely that the mechanism *per se* has a direct relationship with myocardial events. Incomplete platelet inhibition has been suggested as a possible further mechanism for the potential

increased MI risk in patients treated with dabigatran,[29] but other studies failed to confirm this hypothesis.[55, 56]

A comparative study of the coronary risks of the different NOACs was performed by Loke *et al.* by means of adjusted indirect treatment comparisons meta-analysis.[46] Most of the weight derived from VKA-controlled trials, and results pointed to an increased risk of acute coronary events with dabigatran compared to rivaroxaban or apixaban. As previously mentioned, there are difference in how VKA were controlled in each trial and that may explain at least some of the variability in the coronary risks of individual NOACs reported in RCTs.

Previous 2010 Canadian Cardiovascular Society guidelines for AF have suggested caution regarding dabigatran use in patients with AF at high risk of coronary events.[57] However, the subsequent recommendations, following the post-hoc evaluation of myocardial events in RE-LY,[34] do not point out such concerns.[58]

The results of ongoing trials with NOACs in patients with AF and coronary disease undergoing PCI with stenting (apixaban: NCT02415400; dabigatran: RE-DUAL PCI NCT02164864; edoxaban: EDOX-APT NCT02567461; rivaroxaban: PIONEER AF-PCI NCT01830543, X-PLORER NCT01442792, GEMINI ACS 1 NCT02293395) will provide in the future further insights about the coronary safety of these drugs.

Thus, current knowledge does not excludes the use of any individual NOAC in patients with AF for the prevention of acute coronary events. Currently, only rivaroxaban 2.5 mg twice daily is approved for the prevention of atherothrombotic events in adult patients after an ACS (without AF).

The overall body of evidence is consistent for an absence of increased coronary risks with apixaban and rivaroxaban. Fewer data is available for edoxaban and strong claims cannot be currently made for this NOAC. On the other hand, there is a need for further evaluation of coronary risks among dabigatran treated patients to establish whether this drug is inferior to VKA. Nevertheless, coronary risks (if significantly increased at all)

should always be balanced with other outcomes, and currently dabigatran seems to provide better protection on total cardiovascular endpoints.[34]

Declaration of Interest

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* Of interest

*Of considerable interest

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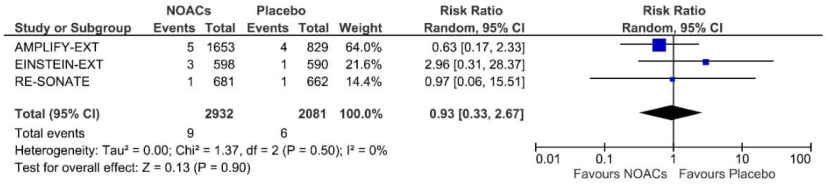


Figure 1: Pooled ACS risk in placebo-controlled trials in VTE patients.

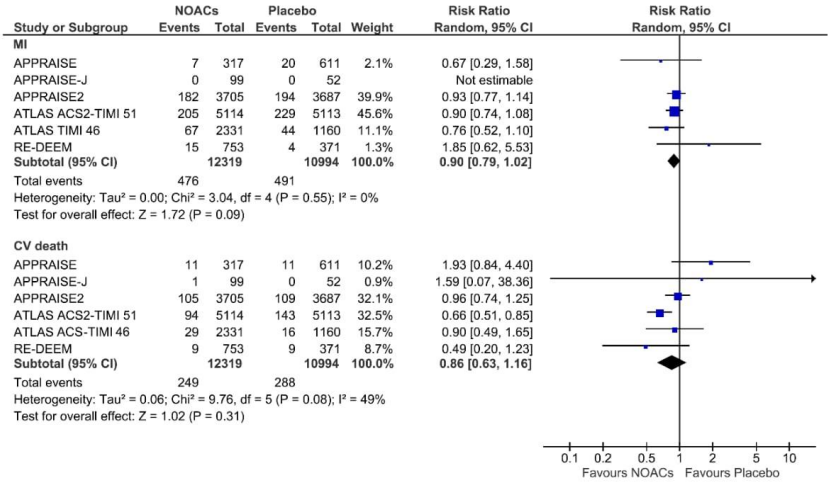


Figure 2: Pooled MI and CV death risks in ACS placebo-controlled trials.

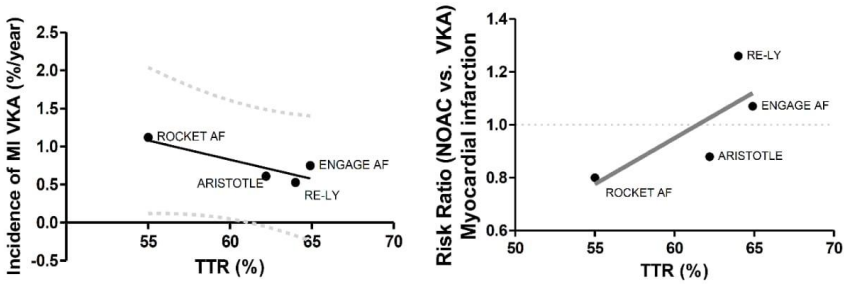
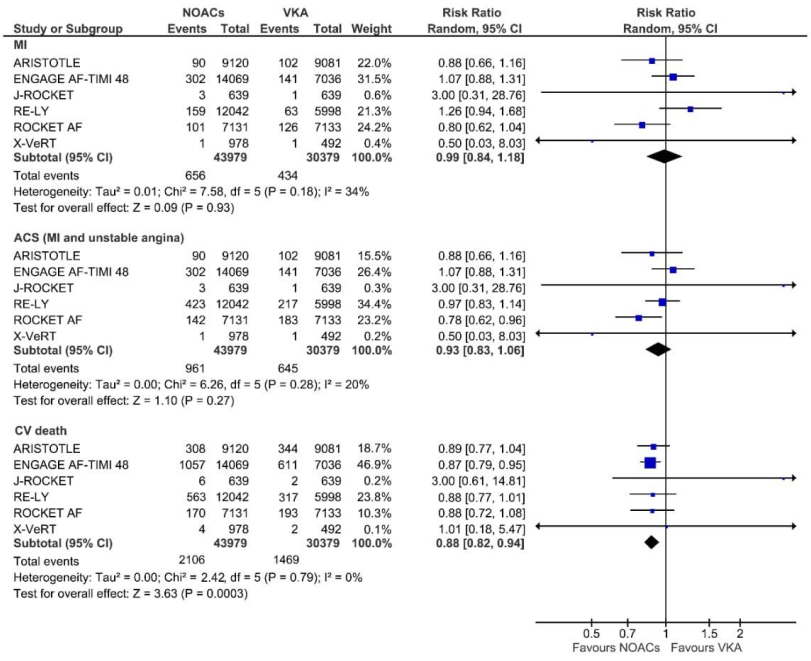


Figure 3: Relationship between MI rates in VKA arms and risk ratio for MI in the pivotal phase III trials of NOACs.



Study or Subgroup	NOACs Events	NOACs Total	VKA Events	VKA Total	Weight	Risk Ratio Random, 95% CI
MI						
ARISTOTLE	90	9120	102	9081	22.0%	0.88 [0.66, 1.16]
ENGAGE AF-TIMI 48	302	14069	141	7036	31.5%	1.07 [0.88, 1.31]
J-ROCKET	3	639	1	639	0.6%	3.00 [0.31, 28.76]
RE-LY	159	12042	63	5998	21.3%	1.26 [0.94, 1.68]
ROCKET AF	101	7131	126	7133	24.2%	0.80 [0.62, 1.04]
X-VeRT	1	978	1	492	0.4%	0.50 [0.03, 8.03]
Subtotal (95% CI)		**43979**		**30379**	**100.0%**	**0.99 [0.84, 1.18]**
Total events	656		434			
Heterogeneity: Tau² = 0.01; Chi² = 7.58, df = 5 (P = 0.18); I² = 34%						
Test for overall effect: Z = 0.09 (P = 0.93)						
ACS (MI and unstable angina)						
ARISTOTLE	90	9120	102	9081	15.5%	0.88 [0.66, 1.16]
ENGAGE AF-TIMI 48	302	14069	141	7036	26.4%	1.07 [0.88, 1.31]
J-ROCKET	3	639	1	639	0.3%	3.00 [0.31, 28.76]
RE-LY	423	12042	217	5998	34.4%	0.97 [0.83, 1.14]
ROCKET AF	142	7131	183	7133	23.2%	0.78 [0.62, 0.96]
X-VeRT	1	978	1	492	0.2%	0.50 [0.03, 8.03]
Subtotal (95% CI)		**43979**		**30379**	**100.0%**	**0.93 [0.83, 1.06]**
Total events	961		645			
Heterogeneity: Tau² = 0.00; Chi² = 6.26, df = 5 (P = 0.28); I² = 20%						
Test for overall effect: Z = 1.10 (P = 0.27)						
CV death						
ARISTOTLE	308	9120	344	9081	18.7%	0.89 [0.77, 1.04]
ENGAGE AF-TIMI 48	1057	14069	611	7036	46.9%	0.87 [0.79, 0.95]
J-ROCKET	6	639	2	639	0.2%	3.00 [0.61, 14.81]
RE-LY	563	12042	317	5998	23.8%	0.88 [0.77, 1.01]
ROCKET AF	170	7131	193	7133	10.3%	0.88 [0.72, 1.08]
X-VeRT	4	978	2	492	0.1%	1.01 [0.18, 5.47]
Subtotal (95% CI)		**43979**		**30379**	**100.0%**	**0.88 [0.82, 0.94]**
Total events	2106		1469			
Heterogeneity: Tau² = 0.00; Chi² = 2.42, df = 5 (P = 0.79); I² = 0%						
Test for overall effect: Z = 3.63 (P = 0.0003)						

Figure 4: Pooled MI, ACS and CV death risks in AF VKA-controlled trials.

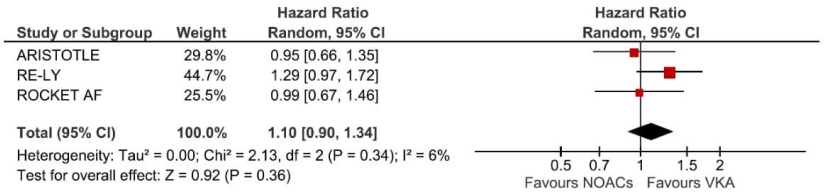


Figure 5: Pooled MI risk in patients with concomitant AF and CAD.

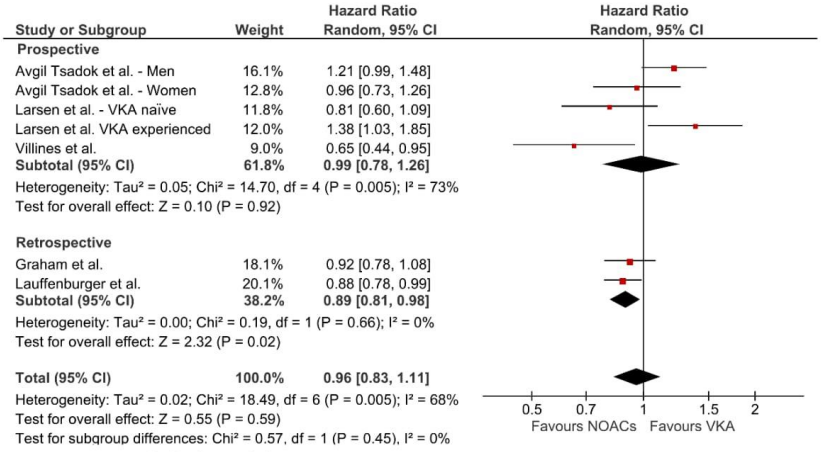


Figure 6: Pooled MI risks with NOACs compared with VKA in observational studies.

Table 1: Characteristics of NOACs placebo-controlled trials.

Year	Study Acronym	Patients (n)	Mean age (years)	Comparison	Follow-Up
Placebo-controlled trials in venous thromboembolism					
2013	AMPLIFY-EXT	2482 patients with VTE who had 6 to 12 months of anticoagulation	57	Apixaban 2.5 mg BID (N = 840) or Apixaban 5 mg BID (N = 813) vs Placebo (N = 829)	12 months
2010	EINSTEIN-EXT	1177 patients with deep venous thrombosis	55	Acute DVT Study: Rivaroxaban 10 mg OD (N = 1731) vs Placebo (N = 1718) Continued Treatment Study: Rivaroxaban 10 mg OD (N = 602) vs Placebo (N = 594)	18 months
2013	RE-SONATE	1363 patients with VTE who had who had 3 months of anticoagulation	58	Active-Control Study: Dabigatran 150 mg BID (N = 1430) vs Placebo (N = 1426) Placebo-Control Study: Dabigatran 150 mg BID (N = 681) vs Placebo (N = 662)	According to intended treatment duration: 6 months (60%), and 12 months (40%)
Placebo-controlled trials in ACS, on top of standard antiplatelet therapy					
2013	APPRAISE	1715 patients with recent ST-elevation or non–ST-elevation ACS	61	6 months of placebo (N = 611) vs 1 of 4 doses of Apixaban: 2.5 mg BID (N = 317), 10 mg OD (N = 318), 10 mg BID (N = 248), or 20 mg OD (N = 221).	6.5 months
2011	APPRAISE-2	7392 patients with a recent ACS and at least two additional risk factors for recurrent ischemic events	67	Apixaban, at a dose of 5 mg BID (N = 3705) vs placebo (N = 3687), in addition to standard antiplatelet therapy	15 months
2009	APPRAISE-J	151 Japanese male and female patients within 7 days of the onset of ACS	64.6	Apixaban at 2 dosages, 2.5 mg BID (N = 49) and 5mg BID (N = 50) vs placebo (N = 52)	6 months
2009	ATLAS ACS-TIMI 46	3491 recent ACS patients treated with aspirin alone (n=761) or aspirin + thienopyridine (n=2730)	57.8	Stratum 1: Rivaroxaban OD or BID (total daily doses: 5, 10, or 20 mg; N = 508) vs placebo (N = 253) Stratum 2: Rivaroxaban OD or BID (total daily doses: 5, 10, 15, or 20 mg; N = 1823) vs placebo (N = 907)	6 months
2009	ATLAS ACS2-TIMI 51	15526 patients with a recent ACS	61.7	Rivaroxaban at dosages of 2.5 mg BID (N = 5174) or 5 mg BID (N = 5176) vs placebo (N = 5176)	31 months
2011	RE-DEEM	1878 patients with recent ACS (ST- or non-ST-elevation MI)	61.9	Dabigatran 4 dosages: 50mg BID (N = 372), 75mg BID (N = 371), 110mg BID (N = 411) and 150mg BID (N = 351) vs placebo (N = 373)	6 months

Sample sizes based on intention-to-treat populations. Meta-analyses considered when possible safety populations.
ACS, acute coronary syndrome; *BID,* twice daily; *DVT,* deep venous thrombosis; *MI,* myocardial infarction; *OD* once daily; *VTE* venous thromboembolism.

Table 2: Characteristics of RCTs evaluating NOACs in AF patients.

Year	Study Acronym	Patients (n)	Mean Age (years)	Comparison	Follow-Up
ASA-controlled trial in non-valvular AF patients unsuitable to VKA					
2011	AVERROES	5599	70	Apixaban 5mg BID (N = 2808) vs ASA 81mg to 324mg (N = 2791)	1.1 years
VKA-controlled trials in non-valvular AF patients					
2011	ARISTOTLE	18201	70	Apixaban 5mg BID (N = 9120) vs dose adjusted Warfarin (N = 9081)	1.8 years
2013	ENGAGE AF	21105	72	Edoxaban 30 mg OD (N = 7034) or Edoxaban 60 mg OD (N = 7035) vs Warfarin OD (N =7036) Target INR 2.0-3.0	2.8 years
2011	J-ROCKET	1278	71	Rivaroxaban 15 mg OD (N = 639) vs Warfarin OD (N = 639) Target INR 2.0-3.0; except >70 years INR 1.6-2.6	>1 year
2009	RE-LY	18113	71	Dabigatran 110mg BID (N = 6015) or Dabigatran 150mg BID (N = 6076) vs Warfarin OD (N = 6022) Target INR 2.0-3.0	2 years
2011	ROCKET-AF	14264	73	Rivaroxaban 20 mg OD (N = 7131) vs Warfarin OD (N = 7133) Target INR 2.0-3.0	1.92 years
2014	X-VeRT	1504 AF patients undergoing elective cardioversion	65	Rivaroxaban 20 mg orally OD (or 15 mg OD in patients with creatinine clearance of 30–49 mL/min) (N = 1002) vs VKA (warfarin or other) (N = 502)	42 days

Table 3: Observational studies of NOACs with incident MI data.

Year	Study	Patients (n)	Mean age (years)	Follow-up	Comparison	MI definition	Outcome adjustments
Prospective studies							
2015	Avgil Tsadok et al.	63110 with AF	78.3	1.3 years	Dabigatran (110 and 150 mg bid) *vs* warfarin	ICD-9/10 codes	Relevant propensity scores, comorbidities, and filled prescriptions.
2014	Larsen et al.	66198 with AF	74.6	16.0 months	Dabigatran (110 and 150 mg bid) *vs* warfarin	ICD-9	Time since initiation of VKA therapy; age; components of CHA_2DS_2-VASc and HAS-BLED; history of any myocardial ischemic event.
2015	Villines et al.	25586 with AF	74	257.3 days	Dabigatran *vs* warfarin	ICD-9 codes	Following propensity score matching, the crude (unadjusted) and adjusted hazard ratios for primary and secondary outcomes were almost all identical.
Retrospective studies							
2015	Lauffenburger et al.	64935 with AF	70.1	2 years	Dabigatran vs warfarin	ICD-9 codes	Age, gender, comorbidities, thromboembolic risk, bleeding risk, concomitant therapy
2014	Graham et al.	134414 with AF	> 65	>181 days	Dabigatran (75 mg and 150 mg bid) *vs* warfarin	ICD-9 codes	Sociodemographic characteristics, baseline medical comorbidities, medications used during the preceding 6 months, prescriber characteristics, and other potentially relevant variables.

Table 4: Systematic reviews with meta-analysis that aimed to determine the coronary risks of NOACs.

Systematic review	NOAC	RCTs (n)	Patients (n)	MI and Cardiovascular Death Risk	Conclusions
Tornyos 2014	Apixaban	12	54054	MI Risk: OR 0.90; 95% CI 0.77–1.05 CV death Risk: OR 0.88; 95% CI 0.72–1.06	Apixaban was not associated with an increased MI or mortality risk, compared to different controls.
Clemens 2013	Dabigatran (only 110 mg, 150 mg doses)	14	42484	*Dabigatran 110 mg* MI Risk: OR 1.30; 95% CI 0.96–1.76 CV death Risk: OR 1.01, 95% CI 0.82–1.25 *Dabigatran 150 mg* MI Risk: OR 1.42; 95% CI 1.07–1.88 CV death Risk: OR 0.89; 95% CI 0.72–1.11	Warfarin was associated with a protective MI effect compared with dabigatran. Dabigatran showed an overall positive benefit-risk ratio for multiple clinically important CV composite endpoints.
Douxfils 2014	Dabigatran	14	40195	MI Risk: OR 1.34; 95% CI 1.08–1.65 All-cause Mortality Risk:OR 0.89; 95% CI 0.80–1.00	Dabigatran was associated with a significantly increase risk of MI.
Uchino 2012	Dabigatran	7	30514	MI/ACS Risk: OR 1.33; 95% CI 1.03–1.71 Mortality Risk: OR 0.89; 95% CI 0.80-0.99	Dabigatran was associated with an increased risk of MI and ACS in a broad spectrum of patients when compared against different controls.
Chatterjee 2013	Rivaroxaban	9	53827	MI Risk: OR 0.82; 95% CI 0.72–0.94 CV death Risk: OR 0.84; 95% CI 0.72–0.97	Rivaroxaban was associated with a significantly lower risk of MI in a broad spectrum of patients when compared against different controls.
Mak 2012	Apixaban, Dabigatran, Rivaroxaban and Ximelagatran***	28	138948	*Apixaban* ACS Risk: OR 0.94; 95% CI 0.82–1.07 *Dabigatran* ACS Risk: OR 1.30; 95% CI 1.04–1.63 *Rivaroxaban* ACS Risk: OR 0.78; 95% CI 0.69–0.89 *Ximelagatran* ACS Risk: OR 1.65; 95% CI 0.56–4.87	The risk for coronary events was significantly higher for dabigatran but not significantly higher for ximelagatran. Conversely, this risk was lower among anti-Xa inhibitors. All-cause mortality was lower among those receiving novel antithrombotic agents.
Oldgren 2013	Apixaban, Dabigatran, Darexaban**, Rivaroxaban and Ximelagatran***	7	30866	*NOAC added to single antiplatelet:* MACE*: HR 0.70; 95% CI 0.59–0.84;* Clinically significant bleeding*: HR 1.79; 95% CI 1.54–2.09* *NOAC added to dual antiplatelet:* MACE*: HR 0.87; 95% CI 0.80–0.95;* Clinically significant bleeding*: HR 2.34; 95% CI 2.06–2.66*	The addition NOACs to antiplatelet therapy results in a modest reduction in cardiovascular events but a substantial increase in bleeding, particularly in patients treated with dual antiplatelet therapy

Loke 2014	Apixaban, Rivaroxaban and Dabigatran	27	132445	*Apixaban* ACS Risk: OR 0.89; 95% CI 0.78–1.03 *Dabigatran* ACS Risk: OR 1.45; 95% CI 1.14–1.86 *Rivaroxaban* ACS Risk: OR 0.81; 95% CI 0.72–0.93 *Apixaban vs. Dabigatran**** ACS Risk: OR 0.59; 95% CI 0.42–0.84 *Rivaroxaban vs. Dabigatran**** ACS Risk: OR 0.52; 95% CI 0.37–0.72	There were significant differences in the comparative safety of apixaban, rivaroxaban and dabigatran regarding ACS risk, being higher for dabigatran in comparison to apixaban and rivaroxaban.

The role of the author in the research projects

The rules for presentation of PhD dissertations in the Faculty of Medicine, University of Lisbon were approved by the Scientific Council in 24th of June 2014.
Details about the role of Daniel Caldeira in the obtention of the results presented in this PhD dissertation are presented ahead as required by the referred document.

Following the principles supported by the International Committee of Medical Journal Editors, Daniel Caldeira had significant roles in the obtention of results presented on this PhD dissertation.

Daniel Caldeira was the main investigator and first author of all projects, with the exception of the research projects of Chapter V.
Thus, essential contributions were made the conception or design of the work, the acquisition, analysis, and interpretation of data for the work, as well as drafting tand revising it critically for important intellectual content. The final versions were approved to be published, ensuring the accuracy and integrity of all parts of the work.
In the Chapter V - Pharmacoeconomic research projects, the author contributed for data generation and analysis. The interpretation of data and critical revisions for important intelectial contents were also performed. The author was a member of the panel of experts required for these research projects.

Authors of the research projects – Research Team

Research projects and research team

Chapter II

The prevalence of oral anticoagulation in patients with atrial fibrillation in Portugal: Systematic review and meta-analysis of observational studies.
Daniel Caldeira[a,b,c], Márcio Barra[a], Cláudio David[a,b], João Costa[a,b,d,e], Joaquim J Ferreira[a,b], Fausto J Pinto[f].

Evaluation of time in therapeutic range in anticoagulated patients: a single-center, retrospective, observational study.
Daniel Caldeira[a,b,c], Inês Cruz[c], Gonçalo Morgado[c], Catarina Gomes[c], Cristina Martins[c], Isabel João[c], Hélder Pereira[c].

Prescription of anticoagulants in Portuguese outpatients: the pattern has changed towards NOACs.
Daniel Caldeira[a,b,c], Daisy de Abreu[a,b], Nilza Gonçalves[a,b], Fausto J Pinto[d], Joaquim J Ferreira[a,b].
Special acknowledgement to Pfizer, IMS Health Portugal and INFARMED for providing data for analysis.

Chapter III

Systematic reviews and meta-analyses evaluating NOACs (see published articles' authorship)
Daniel Caldeira[a,b,c], Filipe Brogueira Rodrigues[a,b], Márcio Barra[a], Mário Canastro[g], Adriana Ferreira[a], Andreia Rocha[a], Ana Augusto[a], Ana Teresa Santos[a,b], Daisy de Abreu[a,b], Nilza Gonçalves[a,b], Fausto J Pinto[d], Joaquim J Ferreira[a,b], João Costa[a,b,d,e].

Chapter IV

Oral anticoagulants data from the national pharmacovigilance database of spontaneous reports.

Daniel Caldeira[a,b,c], Raquel Rodrigues[a], Daisy de Abreu[a,b], Ana Marta Anes[a,b], Joaquim J. Ferreira[a,b], Mário M. Rosa[a,b].

Chapter V

Gouveia M, Costa J, Alarcão J, Augusto M, Caldeira D, Pinheiro L, Vaz Carneiro A, Borges M. Burden of disease and cost of illness of atrial fibrillation in Portugal.

Miguel Gouveia[e,h], João Costa[a,b,d,e], Joana Alarcão[e], Margarida Augusto[e], Daniel Caldeira[a,b,c], Luís Pinheiro[i], António Vaz Carneiro[e], Margarida Borges[a,b,e,j].

Cost-effectiveness of the non-vitamin K antagonist oral anticoagulants for Atrial Fibrillation in Portugal.

João Costa[a,b,d,e], Francesca Fiorentino[e], Daniel Caldeira[a,b,c], Mónica Inês[k], Catarina Pereira[e], Luis Pinheiro[i], António Vaz Carneiro[e], Margarida Borges[a,b,e,j], Miguel Gouveia[e,h].

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Search strategies for the systematic reviews presented in the Chapter III

Search strategies for OVID/MEDLINE:

3.2.1. Major bleeding, fatal bleeding events and major bleeding-related mortality

#	Searches
1	exp mortality/
2	exp Fatal outcome/
3	exp Hemorrhage/
4	(major adj2 (bleed* or hemorrhag* or haemorrhag*) adj3 (fatal or mortality or death)).af.
5	1 or 2
6	3 and 5
7	4 or 6
8	new oral anticoagulant*.af.
9	noac*.af.
10	apixaban.af.
11	dabigatran.af.
12	rivaroxaban.af.
13	edoxaban.af.
14	noac.af.
15	eliquis.af.
16	pradaxa.af.
17	lixiana.af.
18	savaysa.af.
19	xarelto.af.
20	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	randomized controlled trial.pt.
22	controlled clinical trial.pt.
23	randomized.ab.
24	drug therapy.fs.
25	randomly.ab.

26	trial.ab.
27	groups.ab.
28	21 or 22 or 23 or 24 or 25 or 26 or 27
29	exp animals/ not humans.sh.
30	28 not 29
31	7 and 20 and 30
32	remove duplicates from 31

3.2.2. Major gastrointestinal bleeding

#	Searches
1	exp Gastrointestinal Hemorrhage/
2	exp Hematemesis/
3	exp Melena/
4	exp Peptic Ulcer Hemorrhage/
5	gastrointestinal hemorrhage.af.
6	Gastrointestinal haemorrhage.af.
7	GI hemorrhage.af.
8	gi haemorrhage.af.
9	gastrointestinal bleed*.af.
10	gi bleed*.af.
11	Hematochezia.af.
12	Haematochezia.af.
13	(peptic ulcer* adj2 (bleed* or hemorrhage or haemorrhage)).af.
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15	dabigatran.af.
16	rivaroxaban.af.
17	apixaban.af.
18	edoxaban.af.
19	pradaxa.af.
20	xarelto.af.
21	eliquis.af.

22	lixiana.af.
23	noac*.af.
24	doac*.af.
25	tsoac*.af.
26	new oral anticoagulant*.af.
27	non-vitamin K oral anticoagulant*.af.
28	non-vitamin K antagonist oral anticoagulant.af.
29	savaysa.af.

3.2.3. Intracranial hemorrhage

#	Searches
1	(intracranial adj2 (bleed* or hemorrhag* or haemorrhag*)).af.
2	exp Cerebral Hemorrhage/
3	exp Intracranial Hemorrhage, Hypertensive/
4	exp Intracranial Hemorrhage, Traumatic/
5	exp Subarachnoid Hemorrhage/
6	exp Hematoma, Epidural, Cranial/
7	exp Hematoma, Subdural/
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	new oral anticoagulant*.af.
10	noac. af
11	apixaban.af.
12	dabigatran.af.
13	rivaroxaban.af.
14	edoxaban.af.
15	darexaban.af.
16	9 or 10 or 11 or 12 or 13 or 14
17	8 and 15
18	randomized controlled trial.pt.
19	controlled clinical trial.pt.
20	randomized.ab.

21	placebo.ab.
22	drug therapy.fs.
23	randomly.ab.
24	trial.ab.
25	groups.ab.
26	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
27	exp animals/ not humans.sh.
28	25 not 26
29	16 and 27

3.2.4. Other major bleeding sites: intraocular hemorrhage

#	Searches
1	exp eye hemorrhage/
2	intraocular hemorrhage.af.
3	intraocular bleeding.af.
4	Choroid Hemorrhage.af.
5	Hyphema.af.
6	Retinal Hemorrhage.af.
7	Vitreous Hemorrhage.af.
8	exp Choroid Hemorrhage/
9	exp Hyphema/
10	exp Retinal Hemorrhage/
11	exp Vitreous Hemorrhage/
12	hemovitreous.af.
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14	dabigatran.af.
15	rivaroxaban.af.
16	apixaban.af.
17	edoxaban.af.
18	pradaxa.af.
19	xarelto.af.
20	eliquis.af.

21	lixiana.af.
22	noacs.af.
23	noac.af.
24	new oral anticoagulant*.af.
25	non-vitamin K oral anticoagulant.af.
26	non-vitamin K antagonist oral anticoagulant.af.
27	darexaban.af.
28	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29	13 and 28

3.2.4. Other major bleeding sites: pericardial hemorrhage

#	Searches
1	Pericardium.af
2	Pericardial.af
3	Pericarditis.af
4	1 or 2 or 3
5	dabigatran.af.
6	rivaroxaban.af.
7	apixaban.af.
8	edoxaban.af.
9	pradaxa.af.
10	xarelto.af.
11	eliquis.af.
12	lixiana.af.
13	noacs.af.
14	noac.af.
15	new oral anticoagulant*.af.
16	non-vitamin K oral anticoagulant.af.
17	non-vitamin K antagonist oral anticoagulant.af.
18	darexaban.af.
19	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20	4 and 19

3.3.1. Drug-induced liver injury*

#	Searches
1	dabigatran.af.
2	rivaroxaban.af.
3	apixaban.af.
4	edoxaban.af.
5	pradaxa.af.
6	xarelto.af.
7	eliquis.af.
8	lixiana.af.
9	noacs.af.
10	noac.af.
11	randomized controlled trial.pt.
12	controlled clinical trial.pt.
13	randomized.ab.
14	placebo.ab.
15	drug therapy.fs.
16	randomly.ab.
17	trial.ab.
18	groups.ab.
19	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
20	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20	19 and 20

*High sensitivity search, without considering the outcome

3.3.2. Renal dysfunction

#	Searches
1	apixaban.af.
2	dabigatran.af.
3	rivaroxaban.af.
4	edoxaban.af.
5	noac.af.
6	noacs.af.
7	1 or 2 or 3 or 4 or 5 or 6

8	atrial fibrillation.ti,ab.
9	exp atrial fibrillation/
10	8 or 9
11	(renal adj2 disease).ti,ab.
12	(renal adj2 failure).ti,ab.
13	(renal adj2 dysfunction).ti,ab.
14	(renal adj2 injury).ti,ab.
15	(kidney adj2 disease).ti,ab.
16	(kidney adj2 dysfunction).ti,ab.
17	(kidney adj2 failure).ti,ab.
18	11 or 12 or 13 or 14 or 15 or 16 or 17
19	randomized controlled trial.pt.
20	controlled clinical trial.pt.
21	randomized.ab.
22	clinical trials as topic.sh.
23	randomly.ab.
24	trial.ti.
25	19 or 20 or 21 or 22 or 23 or 24
26	exp animals/ not humans.sh.
27	25 not 26
28	7 and 10 and 18 and 27

3.3.3. Insomnia and 3.3.4. Infections*

#	Searches
1	dabigatran.af.
2	rivaroxaban.af.
3	apixaban.af.
4	edoxaban.af.
5	pradaxa.af.
6	xarelto.af.
7	eliquis.af.
8	lixiana.af.
9	noacs.af.
10	noac.af.
11	randomized controlled trial.pt.
12	controlled clinical trial.pt.
13	randomized.ab.
14	placebo.ab.
15	drug therapy.fs.
16	randomly.ab.
17	trial.ab.
18	groups.ab.
19	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
20	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20	19 and 20

*High sensitivity search, without considering the outcome

Main characteristics of studies included in the Chapter III

Main characteristics of phase III RCTs comparing NOACs with VKA (with or without LMWH).

Year	Study Acronym	Patients	Mean/ Median Age		Comparison	Follow up	Primary outcome
Atrial fibrillation							
2011	ARISTOTLE	18201 patients with nonvalvular AF	70		Apixaban 5mg BID vs Warfarin	1.8 years	Stroke or systemic embolism
2009	RE-LY	18113 patients with nonvalvular AF	71		Dabigatran 110mg BID vs Dabigatran 150mg BID vs Warfarin	2 years	Stroke or systemic embolism
2011	ROCKET-AF	14264 patients with nonvalvular AF	73		Rivaroxaban 20 mg OD vs Warfarin	23 months	Stroke or systemic embolism
2011	J-ROCKET	1278 patients with nonvalvular AF	71		Rivaroxaban 15 mg OD vs Warfarin, except >70 years Target INR for >70 years 1.6-2.6	>1 year	Stroke or systemic embolism
2013	ENGAGE AF	21105 patients with nonvalvular AF	72		Edoxaban 60 mg OD or Edoxaban 30 mg OD vs Warfarin	2.8 years	Stroke or systemic embolism
Venous thromboembolism							
2013	AMPLIFY	5395 patients with acute VTE	57		Apixaban 10 mg BID for 7 days, and then 5 mg BID for 6 months vs subcutaneous enoxaparin, followed by VKA	6 months	VTE events or VTE-related death
2013	RE-MEDY	2856 patients with VTE with 3 months of anticoagulation	55		Dabigatran 150 mg BID vs Warfarin OD Target INR 2.0-3.0	6 months	VTE events or VTE-related death
2013	Hokusai-VTE	8240 patients with VTE	56		Edoxaban 60 mg OD vs Warfarin	8.2 months	Recurrent symptomatic VTE
2009	RE-COVER	2539 patients with acute proximal VTE	55		Dabigatran 150 mg BID vs Warfarin	30 days	VTE events or VTE-related death
2014	RE-COVER II	2161 patients with acute VTE	55		Dabigatran 150 mg BID vs Warfarin	6 months	VTE events or VTE-related death
2010	EINSTEIN Acute DVT	3330 patients with acute DVT	56		Rivaroxaban 15 mg BID for 3 weeks and 20 mg OD afterwards vs subcutaneous enoxaparin, followed by VKA	According to intended treatment duration: 3 months (12%), 6 months (63%), and 1 year (25%)	Recurrent VTE events
2012	EINSTEIN–PE	4832 patients with symptomatic PE	58		Rivaroxaban given 15 mg BD for 3 weeks, followed by 20 mg OD vs subcutaneous enoxaparin, followed by VKA	According to intended treatment duration: 3 months (5%), 6 months (57%), and 1 year (38%)	Symptomatic recurrent VTE

AF: Atrial fibrillation; BID: twice daily; DVT: Deep venous thrombosis; OD: once daily; PE: Pulmonary embolism; VE: Venous thromboembolism; VKA: Vitamin K antagonist.

Main characteristics of phase III RCTs comparing NOACs with non-VKA controls.

Year	Study Acronym	Patients	Mean/Median Age	Comparison	Follow up	Primary outcome
			Atrial fibrillation			
2011	AVERROES	5599 patients with non-valvular AF, unsuitable to VKA	70	Apixaban 5mg BID vs Aspirin 81mg to 324mg per day	1.1 years	Stroke or systemic embolism
			Venous thromboembolism			
2013	AMPLIFY-EXT	2482 patients with VTE who had 6 to 12 months of anticoagulation	57	Apixaban 2.5 mg BID vs Apixaban 5 mg BID vs Placebo	1 year	VTE events or VTE-related death
2013	RE-SONATE	1363 patients with VTE with 3 months of anticoagulation	55	Dabigatran 150 mg BID vs Placebo	18 months	VTE or VTE-related death associated with VTE
2010	EINSTEIN Continued Treatment Study	1177 patients with DVT	58	Rivaroxaban 10 mg OD vs Placebo	According to intended treatment duration: 6 months (60%), and 1 year (40%)	Recurrent VTE events
			Hip and Knee Surgery			
2009	ADVANCE-1	3184 patients who underwent total knee replacement	66	2.5 mg of apixaban BID vs 30 mg of subcutaneous enoxaparin BID	60 days after anticoagulation period	VTE events and all-cause mortality
2010	ADVANCE-2	3009 who underwent elective total knee replacement	67	2.5 mg of apixaban BID vs 40 mg of subcutaneous enoxaparin OD	60 days after anticoagulation period	VTE events and all-cause mortality
2010	ADVANCE-3	5332 patients who underwent total hip replacement	61	2.5 mg of apixaban BID vs 40 mg of subcutaneous enoxaparin OD	60 days after anticoagulation period	VTE events and all-cause mortality
2007	RE-NOVATE	3494 patients who underwent primary elective unilateral total hip replacement	64	Dabigatran 220 mg OD vs Dabigatran 150 mg vs Enoxaparin 40 mg OD	2 and 3 months after surgery	VTE events and all-cause mortality
2007	RE-MODEL	2076 patients who underwent unilateral total knee Replacement	68	Dabigatran 220 mg OD vs Dabigatran 150 mg OD vs Enoxaparin 40 mg OD	3 months	VTE events and all-cause mortality
2009	RE-MOBILIZE	2596 patients who underwent Unilateral total knee arthroplasty	66	Dabigatran 220 mg OD vs Dabigatran 150 mg OD vs Enoxaparin 30 mg BID	3 months	VTE events and all-cause mortality
2011	RE-NOVATE II	2013 patients who underwent primary, unilateral, elective total hip arthroplasty	62	Dabigatran 220 mg OD vs Enoxaparin 40 mg OD	3 months	VTE events and all-cause mortality

2008	RECORD1	4257 patients who underwent elective total hip arthroplasty	63	Rivaroxaban 10 mg OD vs Enoxaparin 40 mg OD	30 to 35 days	Deep-vein thrombosis, pulmonary embolism and death
2008	RECORD2	2457 patients who underwent elective total hip arthroplasty	62	Rivaroxaban 10 mg OD vs Enoxaparin 40 mg OD	30 to 35 days	VTE events and death
2008	RECORD3	2459 patients who underwent total knee arthroplasty	68	Rivaroxaban 10 mg OD vs Enoxaparin 40 mg OD	30 to 35 days	VTE events and death.
2009	RECORD4	3034 patients who underwent total knee arthroplasty	65	Rivaroxaban 10 mg OD vs Enoxaparin 30 mg BID	30 to 35 days	VTE events and death
				Acute Medical Illness		
2013	MAGELLAN	6998 patients hospitalized for an acute medical illness	71	Rivaroxaban 10 mg OD vs enoxaparin 40 mg OD during 10 days and placebo afterwards	35 days	VTE events
				Acute Coronary syndrome		
2011	APPRAISE-2	7315 patients with recent acute coronary syndrome	67	Apixaban 5 mg BID vs Placebo	241 days	CV death, myocardial infarction, or ischemic stroke
2012	ATLAS ACS 2–TIMI 51	15526 patients with recent acute coronary syndrome	62	Rivaroxaban 2.5 mg BID vs Rivaroxaban 5 mg BID vs Placebo	13 months	Cardiovascular death, myocardial infarction, or stroke

AF: Atrial fibrillation; BID: twice daily; DVT: Deep venous thrombosis; OD: once daily; PE: Pulmonary embolism; VE: Venous thromboembolism; VKA: Vitamin K antagonist.